Rarest of Them All: Ultra-Rare Rheumatic Diseases – Part 1

Transcript

Jonathan Miner, MD (Guest): I think the most important thing, in terms of identifying rare disease, is first taking a good family history; this helps to identify inherited diseases. And, listening carefully to the patients and their stories.

Meghna Rao (Host): Welcome to *Rheum Advisor on Air*, the official podcast of *Rheumatology Advisor*, one of Haymarket Media's leading publications that focuses on the latest news and research in rheumatology to inform clinical practices. I'm your host, Meghna Rao, the editor of *Rheumatology Advisor*.

In this podcast series, we will be looking at emerging topics in the field of rheumatology from various experts. These perspectives may be related to the diagnosis and treatment of rheumatic diseases, current guidelines, practice management, patient care, and much more.

Meghna: Multisystem autoimmune rheumatic diseases are rare or ultra-rare disorders and have been linked to significant mortality and morbidity. However, with the rise of new technology, including data registries and advanced genetic analysis, rare rheumatic disease research is certainly being propelled in a forward direction – that is to inform future therapeutic options and improve patient outcomes.

My guest today is one with a long list of accolades in the field of both rheumatology and infectious diseases. Dr Jonathan Miner is a rheumatologist and an assistant professor of medicine, molecular microbiology, and pathology and immunology at the Washington University School of Medicine in St. Louis, Missouri.

In this episode, we will be discussing his work in the rare disease space and more. It's an honor to speak with you, Dr Miner.

Dr Miner: It's great talking to you, too.

Meghna: Thank you for joining me to talk about what really is a niche, but important, area of science and medicine, ultra-rare rheumatic diseases, which have truly been nature's mysteries. I'm quoting from the Miner Lab website here, by the way! But, tell us, Dr Miner, why and how is rare disease research relevant in rheumatology in the current times?

Dr Miner: We know a lot already about our genes and the proteins that are encoded by them, but there are still far more questions than answers. Our DNA is essentially a blueprint for the human body. There are 20,000 genes,

and each gene is the code for a single protein, and the proteins are really the machinery that make the human body work. I think everyone here knows about The Human Genome Project. It was a huge undertaking that began in 1990; it was completed in 2003. The entire human genome was sequenced. The cost of that project was about $5 billion, adjusted for inflation, and it took more than a decade, but it opened up innumerable opportunities for discovery and led to the development of many novel technologies.

Now, about 20 years later, after completing sequencing of the human genome, we have the capability to sequence our own patient's genomes, and we can do it rapidly, in a matter of weeks, and at a low cost. And, that's leading to a revolution in terms of opportunities for personalized medicine.

My lab is focused on the discovery and the careful characterization of human disease-causing mutations, with the ultimate goal of helping these patients who have ultra-rare diseases, but also with the goal of unraveling mysteries of human biology.

Meghna: Absolutely! I'm glad we're having this conversation. It couldn't have been better timed since today is also being acknowledged as Rare Disease Day.

Now, your work over the last decade or so has primarily included examining the overlap between immunodeficiencies and autoimmune conditions, at a genetic and molecular level. [O]ne of the most intriguing pieces of research and something you presented at the recent [American College of Rheumatology] (ACR) meeting was the mechanisms involved in [Stimulator of Interferon Genes] (STING)-associated vasculopathy with onset in infancy. I'm going for tough ask here, Dr Miner, but can you summarize your findings from [that] set of studies? What does this ultra-rare genetic disease entail, and what have you and your team learned about its immunopathogenesis?

Dr Miner: STING-associated vasculopathy with onset in infancy, or SAVI, is one of these ultra-rare diseases, it was first identified and described by a group at [National Institute of Health] (NIH), led by Raphaela Goldbach-Mansky. This is a disease that is thought to be mediated by a protein called type I interferon, which is very important in antiviral immunity. Now, the disease-causing mutation in SAVI is in a gene called STING. STING is a sensor of viral DNA, and it's very important in responding to a variety of human pathogens, including viruses, and also bacteria. Patients [who] have these mutations in STING have a constitutively active STING protein, which means it's active, even in the absence of any virus stimulus.

The consequence of that is that [the patients] develop life-threatening disease. They develop lung pathology; they have lymphopenia, so low numbers of T cells. We subsequently found that they also have low numbers of innate lymphoid cells. And, using an animal model that has the same mutation that many of the patients have, we discovered that, in animals, the disease is actually not mediated by type I interferon; it occurs independently

of type I interferon. This was [perhaps] one of the most unexpected discoveries – that in an animal model we were able to prove, genetically, that the disease pathogenesis occurs independently of a molecule that was thought to be critical in the disease in humans.

Now, this could be explained through a variety of approaches. One possibility is that humans and animals are different. But, another possibility is that perhaps the disease in humans may also be independent of type I interferon. So, there are many, many different [ongoing] studies looking at how microbes interact with STING to influence disease pathogenesis, and many, many additional experiments that are ongoing to understand exactly how, at the molecular level, STING is causing this terrible disease.

Meghna: Dr Miner, I also wanted to get your thoughts on another devastating, rare genetic disease on your radar, [retinal vasculopathy with cerebral leukoencephalopathy] (RVCL) that I've read affects only a few hundred people. But, since there's currently no cure for this disease, how can ongoing research in the area inform therapeutic options in the future?

Dr Miner: RVCL stands for retinal vasculopathy with cerebral leukoencephalopathy. There are only about 40 families in the entire world that we know of that have this disease. It's an autosomal dominant disease. It's inherited, and it results in relentless damage to multiple organs, onset around age 40 [years]. 100% of these patients die within 5 to 10 years of disease onset. There is currently no effective treatment for it. This disease, RVCL, is caused by mutations in *TRX-1*, which is a protein that actually interacts with STING in the same pathway. We do not know how these mutations in *TRX-1* cause RVCL, and this is one of the major limitations in terms of identifying a treatment. But, we know the genetic cause of disease, and we're beginning to understand more and more about disease pathogenesis.

What we know for sure is that, in RVCL, there is loss of blood flow through small blood vessels, and this led us to our second clinical trial, using a drug called crizanlizumab, which is a monoclonal antibody that targets an adhesion molecule on the vascular endothelium to help prevent microvascular occlusion. So, our hope is that this will prevent ischemia-related organ damage that leads to severe disability, blindness, multiorgan damage, and brain lesions, ultimately dementia and death in these patients.

Meghna: I also heard the story of the family who were thought to be cursed because they had RVCL for many, many years before it was identified, and I think there's an important message that underscores this – that is the importance of screening for and diagnosis of rare diseases, and its clinical implications.

Dr Miner: Yeah, I agree. I think the most important thing in terms of identifying rare diseases is first taking a good family history; this helps to

identify inherited diseases. And, listening carefully to the patients and their stories.

In the case of RVCL, every one of these patients has a family story that is remarkable. For example, they might say my uncle died from a brain tumor; my aunt died from lupus that affected her brain; [or], my father had severe multiple sclerosis. When, in fact, it was really all the same disease. So, their stories are also similar to each other. Listening to that story opens doors in terms of more precisely identifying the disease.

In fact, in all patients with RVCL, the answer can be identified at the genetic level. But, in many cases, what happens with these patients is they begin to undergo a variety of diagnostic procedures, which can include brain biopsies or excision of brain lesions, which are thought to be possibly malignant. After excision of these brain lesions, they realize that there was no evidence of malignancy, it was not any form of cancer, and the genetic test sometimes comes later. When in fact, I think on the basis of family history alone, it may be enough to start genetic testing upfront and spare patients certain diagnostic testing.

Now, one of these families was from Mexico. In their village, the story had been that their family had been cursed for generations, because so many people would die prematurely from a variety of diseases. When we received the referral to see this patient, fortunately some physicians had already done the genetic testing and had identified the disease-causing mutation. For this patient, the disease was already severely progressed, but many of these patients have children, and they know the potential that this disease could be inherited. So, really, having an answer for the family is profoundly important. It allows the next generation to plan, to consider whether they would like to also have a genetic test, to participate in clinical trials, and perhaps also, in many cases, most importantly, it gives patients the option of considering in vitro fertilization with genetic testing, which for inherited disease, especially these ultra-rare diseases, it could be enough to completely eradicate the diseases.

Before the disease-causing mutation was identified by John Atkinson here at Washington University back in 2007, patients didn't have these options. They didn't know the genetic cause of their disease. Now, there are numerous options.

Meghna: That makes a lot of sense, and I think you kind of answered my next question about the effect that SAVI and RVCL have on patients. But, [h]ow can providers [o]pen up the dialogue with these patients? Because these patients are overwhelmed and maybe even scared that they have such a rare genetic disease.

Dr Miner: My approach to this is to, first of all, focus on the opportunities that we have. Delivering news that a patient has one of these devastating disease-causing mutations, especially when they're getting genetically tested

prior to onset of disease, is one of the most difficult things that I have had to do. It is heartbreaking to have to tell a patient that they have one of these disease-causing mutations, especially when they have seen how their own family members have suffered and died prematurely.

But, when we tell them their diagnosis, I tend to take every opportunity I can to focus on the positive aspects of this as well. We know the genes and proteins that cause these specific diseases and that means we have therapeutic targets. So, now, we are working as hard as we can with medicinal chemists and others, not only in terms of repurposing already-approved medications to try to treat these diseases, but also to develop new medications that are personalized for these patients, that target the relevant gene or protein. And, that is the opportunity. I don't know when RVCL is going to be affectively treated or cured, but I know it's going to happen. I don't know whether it'll be in 5 years or 15 years or 30 years, but having that genetic information makes me confident that we're going to find solutions for these patients, and that gives them hope. I'm careful not to give false hope because we don't know when it's going to happen, but there is some hope, and that is what I cling to, and many of the patients also are encouraged by.

Meghna: That's amazing! I absolutely love your positive outlook on this.

Organizations like the NORD, the National Organization for Rare Disease, are committed to raising awareness for [r]are diseases. But, I think researchers, clinicians, and the community are also responsible for continuing to have these conversations about the unknown, exploring the unexplored, and finding answers to those compelling questions. Dr Miner, what's your take on how rare disease research in rheumatology can be advanced?

Dr Miner: I've often wondered if many of our diseases are rare diseases at a genetic level. What I mean to say by that is that it's entirely plausible that many of our patients with more common diseases also have rare mutations that are contributing to disease pathogenesis. The way I try to look at it is to consider the possibility that all of our patients, on some level, may have a form of a rare disease, and certainly, all of our patients are unique.

So, one way I think to approach this, clinically, is for all of us to consider that possibility that our patients may give us opportunities, and some of those opportunities would be to help advance the field, in terms of identifying disease-causing mutations, and also give back to our patients by helping them understand what may be driving their disease.

I think that one of the big challenges is that now we're able to obtain lots of genetic information on patients, but knowing what to do with that information is another story. One of the biggest obstacles for rare diseases in general is that our understanding of the genome is still actually at a very early stage. There's so much left to be discovered. So, work on fundamental mechanisms and fundamental biology, which I think has been the triumph of biomedical research in America; our willingness to try to understand human

biology, even when we do not know yet how it might be relevant for human disease. When we talk about RVCL or SAVI, the genes involved in these diseases were identified by people who were trying to understand antiviral immunity, not necessarily by people who were trying to understand autoimmunity.

I think that what we can do is work together as clinicians and scientists to do everything we possibly can to both advance human knowledge and improve patient care and share information.

One of my great colleagues who is in Houston at Baylor College of Medicine recently told me about a patient who had devastating disease and a mutation that she'd identified and wondered if that mutation might be causing the disease. It happened to be in a gene that my laboratory works on, and sure enough, it's a disease-causing mutation. Then, I reached out another scientist at University of Washington who also has expertise in this gene, and he said, you know, this is a real opportunity for gene therapy in this particular patient, and here's why. This happens simply with people taking initiative and pushing things forward and reaching out to experts.

The hope is that we'll not only be able to help that kid, but there will be others in the future or around the world who would benefit from our increased understanding of what's happening here in that particular disease.

Meghna: You're absolutely right. There's no doubt your lab and others in this space are taking this to the next level. Just to add [t]o what you said, I think improving clinical trial participation and advocating for orphan drug status for treatment thereafter maybe be a valuable asset.

Dr Miner: Absolutely. Our experience has been very positive in that regard, with these ultra-rare diseases. There are many people, both in industry and academia, who are willing to help, if we just take the initiative to make things happen.

Meghna: Amazing! With that, I truly appreciate your time and contributions to the area of ultra-rare diseases in rheumatology, and I will continue to look forward to your work, Dr Miner.

Dr Miner: Thank you very much.

Meghna: Please stay tuned for more episodes in this series. For more information on Rheumatology Advisor and this podcast, you can reach out to us at editor@rheumatologyadvisor.com. We, at *Rheumatology Advisor*, look forward to delivering timely, evidence-based news to you. You can also sign up for our free newsletters on the site.