In Rare We Care: Pediatric Rheumatic Disease Awareness & Management

Transcript

Emily von Scheven, MD (Guest): We really think that there's an opportunity for every patient to teach us something.

Vincent Del Gaizo (Guest): But really, the important thing with shared decision-making is to make sure that the family's needs are met as best they can be.

Meghna Rao (Host): Welcome back to season 2 of the *Rheumatology Advisor* podcast, Rheum Advisor on Air. I'm Meghna Rao, the senior editor of *Rheumatology Advisor* and the host of this podcast.

In this series, we will be joined by expert clinicians and researchers to discuss emerging and compelling topics in rheumatology. These perspectives may be related to the management of rheumatic disease, guideline updates, patient care, data from conferences and scientific meetings, and much more.

So, let's dive in!

Meghna: While juvenile idiopathic arthritis [(JIA)] and lupus are the most common rheumatic diseases in children, more than 500,000 children develop other rheumatic diseases. The diagnosis, treatment, and management of these conditions often require a multidisciplinary approach owing to the diverse clinical manifestations that present in this patient population.

In light of Rare Disease Day, to get varying perspectives on the subject, I'm speaking with Dr Emily von Scheven, a pediatric rheumatologist at the University of California San Francisco Benioff Children's Hospital and the executive committee chair of [Childhood Arthritis and Rheumatology Research Alliance] (CARRA). We're also joined on this episode by Vincent Del Gaizo, director of partnerships and patient engagement for CARRA and a parent of a pediatric patient with rheumatic disease.

Hello to the both of you, and thank you for being a part of this conversation.

Vincent: Glad to be here.

Dr von Scheven: It's great to be here. Thank you so much for your interest in pediatric rheumatology.

Meghna: Of course. Let's start with you, Dr von Scheven. In the US, we all know that a rare disease is defined as a condition affecting fewer than 200,000 individuals. But speaking specifically in terms of pediatric

rheumatology here, how rare is rare? And can you tell us about some of the more rare rheumatologic conditions that present among children?

Dr von Scheven: Yes, thank you for asking. So yeah, that definition comes from the Orphan Drug Act, which was a law put in place to try and incentivize the development of drugs to treat rare diseases because, as you know, they often don't garner enough attention from drug developers and other places as well.

Essentially, all pediatric rheumatic diseases are rare. The most common of them is juvenile idiopathic arthritis, but really that's multiple diseases; it's a family of diseases. The second and third most common would be systemic lupus erythematosus and juvenile dermatomyositis, which are much less common than JIA. And then, there [are] many other conditions as well that are exceedingly [rarer], such as the different forms of vasculitis, [Sjögren] syndrome, [sarcoidosis], [and] chronic recurrent multifocal osteomyelitis.

So, it's a family of diseases, which we often put together because of some of their common features, and we take care of them all as pediatric rheumatologists, but each one is, on its own, extremely rare.

Meghna: We do acknowledge the fact that every rare condition that you mentioned is complex and probably has its own unique set of challenges, right? But I guess to put it loosely, the 3 aspects of rare disease care can be narrowed down into, say, timely diagnosis, appropriate treatment, and health care access.

Dr von Scheven, to get a little bit more specific to pediatric rheumatology, I'd like to get your thoughts on the existing barriers that have a direct impact on the provision of quality patient care?

Dr von Scheven: Yeah, as you said, there are many different barriers in different areas. Access to pediatric rheumatologists, to the subspecialists who are best prepared and trained to take care of these children, is a big challenge because there are just not enough of us around. We tend to work in large medical centers, so there [are] big geographic areas of the country where there's no pediatric rheumatologist. In fact, there are some states that still do not have pediatric rheumatologists, which means that patients and families are left with traveling pretty extensively, sometimes, to find a provider. Vincent can tell you a little bit about how this [affected] his family's journey in terms of getting to a diagnosis.

The other barriers relate to lack of drugs. We're making a lot of progress in the recent era in terms of the development of biologics and other new drugs, but the lack of medications that are really specific for these diseases is also a barrier for obtaining treatment that's effective.

The other barrier is a lack of an evidence base to guide treatment. We don't have a lot of clinical trials happening historically [among] children with rheumatic diseases. We really need to do more research to understand the

best approach to treating these patients and [g]et to figuring out what drug is right for what patient, really getting to precision medicine.

I think there are also barriers in terms of what's happening at the clinical centers. Pediatric rheumatology is a poorly reimbursed subspecialty, mostly because we don't perform a lot of procedures, which are the main ways that health care is compensated.

Meghna: At this time, I also want to bring in the thoughts of Vincent, a parent of a patient with a pediatric rheumatic disease who was faced with some of these challenge before receiving a diagnosis for his child.

Hi there, Vincent. How are you doing?

Vincent: Yes, hi. How are you?

To kind of piggyback off of what Emily was talking about, we had a very similar experience in our diagnostic journey.

So, my son was [aged] 15 months when he first got sick and he presented with the standard illness that kids get. He had fever and he had rash. He was brought to his pediatrician who prescribed antibiotics, and then, it didn't get better. He was tested and treated for pretty much everything under the sun. Then finally, after about 3 weeks, they stopped testing and treating and they were just waiting for him to get better. And we, his dad and my wife, his mom, basically went to the doctors and said, "Look, you're waiting for him to get better, he's not getting better; we need you to either test him or treat him for something else; try something else." A decision was made at that point to send him to another hospital where he received his diagnosis very quickly because he came across somebody who had seen this before.

So, along the lines of what Emily was talking about with barriers, 1 of the barriers that I have noticed in my journey, over [a period of] the last 20 years, is parents and caregivers have to be self-advocates and be able to request that your child gets seen and gets diagnosed.

Meghna: Yeah, I'm sure that was an incredibly frustrating journey in the beginning, but thank you for sharing that with us.

So, what I'm also hearing here is the importance of communication and a shared decision-making process between patient and provider in, of course, all clinical specialties, but especially, rare disease care, right?

Vincent: Yes, absolutely.

A very quick story about shared decision-making: My son [was getting] older and doing better, but he was having a problem with 1 of his feet. So, he had active disease in his foot, and it was causing him some problems, and he [started receiving] a treatment that his condition responded to very, very well. But it had some side effects for him that were not very well tolerated – he lost his appetite and a tremendous amount of weight.

And so, when he was at the clinic and being examined by the doctor, the doctor was very excited that the treatment was working because the disease was out of his foot. He basically said to her, “Yes, it’s working for my arthritis, but it’s not working for me.” Fortunately, the doctor changed his treatment and we found something else that worked on his condition and allowed him to play hockey.

But really, the important thing with shared decision-making is to make sure that the family’s needs are met as best they can be, and you don’t know what those needs are unless you have good communication and shared decision-making.

Meghna: Yes, absolutely, and again, thank you for sharing that little story with us.

To talk a little bit more about the value of meaningful clinical research in rare pediatric rheumatic disease. With the advent of precision medicine, we are on the road to developing more individualized care plans for these patients, right?

Dr von Scheven, how far away are we from implementation of these approaches to pediatric rheumatology? What are your general thoughts on, you know, its feasibility and effectiveness for the rarer conditions?

Dr von Scheven: Yes, I think this is really important and this is really the future and where we need to go. I mean, precision medicine is really predicated on having an understanding of the patient-level differences, understanding the disease biology, and what’s happening in each patient; not only to understand what drug is going to work, but also, to understand what drug is going to be tolerated.

Research is a critical driver for this and it’s harder to do with rare diseases. We really need to pool data across many, many different clinical sites in order to get enough information and enough patients to interpret the data. We also need to have biologic specimens from our patients who are participating in research studies, which is why, through CARRA, the research organization, we’ve built a registry of clinical data and also a biobank, so that patients can contribute their blood or urine or other biospecimens in addition to contributing their data.

I think in terms of how this is playing out in the pediatric rheumatic diseases, you can see some examples of this happening. So, for example, in systemic juvenile idiopathic arthritis, 1 subtype of JIA, those patients we learned did not respond as well to [tumor necrosis factor] (TNF) inhibitors, 1 of the first biologics that was created. But then, we learned that they respond really well to the medications that target IL-1, interleukin-1 (anakinra and Kineret is an example of that medication). And now, it’s become standard practice. So, as we learned about the biology underlying the disease, we could then be smarter about picking the right medication.

Another example is some of the patients where genetic causes are identified as the cause of their condition. This is especially true for patients who have monogenic diseases where specific gene defects cause them to have an autoimmune disease, and this is sometimes seen in some forms of lupus. Not very common, not most patients with lupus, but there are examples of very, very young children who develop lupus and who have this as a result of a gene abnormality that can actually be corrected with a bone marrow transplant.

So, I think that we're going to see more and more of precision medicine entering our routine practice as we learn more about the individual differences between patients and the biology driving their disease. It's very exciting!

Meghna: Yeah, very interesting. A quick question there, piggybacking on what you said, and something I'm personally curious about as well, is what can we, in pediatric rheumatology, learn about drug development and management of pediatric disease from other specialties, for example, childhood cancers?

Dr von Scheven: I think we can learn a lot, and, in fact, a lot of what we've been talking about is something that has been done in the cancer arena, both for pediatric cancer and adult cancer.

So, the childhood cancer community was also very systematic in how they treated their patients [and] developed a standardized approach to treating, and then, as they learned what worked, [they] would refine that. As they learned what specific characteristics of individual children's tumors were associated with particular benefit, with particular medicines, they started to develop more targeted treatments. Similarly in breast cancer, right? The therapy is often determined by the type of tumor you have. So again, that comes back to understanding the biology of the disease.

It turns out the biology of autoimmunity is very complicated. We have a lot of work to do. But I think there are learnings that come from seeing how this has been handled in other disciplines.

Meghna: Right. Just talk a little bit about the CARRA consensus treatment plans or CTPs as an alternative to randomized control clinical trials. On *Rheumatology Advisor* in November last year, we reported a study on the favorable 24-month outcomes observed among children with polyarticular JIA, as a part of the STOP-JIA study, conducted by researchers on behalf of CARRA. We had spoken with Dr Yukiko Kimura, too, regarding this in 1 of our previous podcast episodes.

But, can you, Dr von Scheven, speak more to the advancements in this area owing to the timeliness and relevance of this approach?

Dr von Scheven: Sure. So, the idea of the consensus treatment plans, which was a concept developed by CARRA, was that we knew that we needed to

understand how to use the medications that we currently have in addition to developing new medicines. Randomized controlled trials, as you know, are very costly. They take a long time, and they are really only limited in generalizability to the types of patients that are enrolled in [these trials].

We really think that there's an opportunity for every patient to teach us something; we wanted to be able to learn from our observational data; we wanted to be able to collect data on lots of patients who weren't in clinical trials and still be able to learn from them.

One of the problems we have with being able to make reliable conclusions from observational data is that there's a lot of treatment variability in terms of how patients are treated and it's difficult to control for all that variability. So, the idea with the consensus treatment plans was to reduce the treatment variability.

That's just happening out in practice, okay? The way providers are treating their patients, to have the community come to consensus on a handful of ways to treat a given clinical scenario. So, instead of 100 different ways of doing things, maybe there would be like 3 ways that people would agree on. And then, if those patients who are treated with 1 of those 3 ways [were] enrolled in the CARRA registry, where we could collect all of their clinical data, then we would be in a position to start to analyze how these 3 different treatment approaches compared and to figure out which one was better.

That's exactly what happened with the STOP-JIA project. They learned a lot about how these treatment pathways compared, and they learned about the importance of treating early, and they also learned that that there were some patients who did well even without getting aggressive treatment up front.

This approach of using consensus treatment plans has a lot of potential utility in rare diseases.

Vincent: If I can just add real [quickly], the exciting thing about STOP-JIA that Emily had mentioned is that these patients are in the CARRA registry, and the CARRA registry plans on following [up with] them for at least 10 years, So, we will be continuing to learn from this group of patients for a long time.

Meghna: Yeah that's so exciting. I guess, lastly –Vincent, feel free to chime in as well – what can different stakeholders, including researchers, caregivers, and providers, do to improve the overall quality of life, the access to care, and awareness of rare pediatric diseases in rheumatology? Could you also speak to some examples of any interventions or strategies that are already in place to serve as examples?

Vincent: So, I can provide a couple. One thing that we do in CARRA is we have very active patient engagement. So, we have families that are helping prioritize research [and] design studies to ensure that they are impactful to families and they are acceptable study designs. Because in rare diseases, you

can't do everything. You don't have the resources. You don't have the patients. You don't have money. So, let's make sure we do the most important things first, and caregivers having a seat at the table helps with that.

In addition, when studies like, for example, the STOP-[JIA] study that you mentioned, when it comes time to publish the results of those studies, families participate in that as well by translating the medical jargon into lay language and sharing that with the community through our great partnerships with advocacy organizations, like the Arthritis Foundation is CARRA's premiere partner.

We have registry newsletters written by patients and parents for patients and parents that share results of projects and what is happening in the field. We have them helping with raising awareness of the studies that are ongoing.

Lastly, there's the externally led patient-focused drug development meeting that CARRA hosted with the Arthritis Foundation. The result of that workshop was the Voice of the Patient report. In that Voice of the Patient report, families share barriers to treatment, barriers to their disease, what their greatest challenges are managing life with these conditions, [and] enrolling in clinical trials. By sharing this information through the Voice of the Patient report, the [US Food and Drug Administration] (FDA) has what it needs to assess risk reward of new therapies.

Dr von Scheven: Vincent highlighted some really important points. I think, as a rare disease community, it's really important that we do things to try and garner more attention and more resources, and that requires a lot of advocacy. So, the advocacy organizations, like the Arthritis Foundation, really have a critical role here in terms of advancing things for patients and for research. I mean, they are the conveners of the patients, right? They create a community for patients. There are kids with these rare diseases [who] have never met another person with this condition and their parents have never met another person with this condition. And so, creating a community for them, for support, [and] for sharing information, is really, really valuable.

The advocacy organizations also play a really important role in terms of liaising with policymakers. There are many ways in which they have a central role here as a stakeholder.

CARRA's partnership with the Arthritis Foundation has been really important. We focus on the conducting the research and the dissemination of the research results, but we work really closely with the Arthritis Foundation. They support our research enterprise and they support our community. They have provided support for building the CARRA registry that you heard has now [more than] 10,000 patients enrolled. They've provided support in building the workforce through fellowship grants to try and get more pediatricians to go into pediatric rheumatology, and even internal medicine providers to go into adult rheumatology.

Similarly, we've worked with the Lupus Foundation of America for [patients with] lupus. They advocated for resources on the Hill to create a grant through the [Centers for Disease Control and Prevention] (CDC), which then CARRA applied for and secured, and will allow us to have probably the largest pediatric lupus cohort in North America in a research program.

So, I think they play a really important part in partnerships between them and practitioners, and partnerships between advocacy organizations and research organizations can be very powerful.

Meghna: I think it's incredible, the idea of patients and caregivers as equal research partners.

This has been such an eye-opening conversation that I'm so glad we had. Thank you both again for taking the time to do this.

Dr von Scheven: Of course, it's our pleasure. We're glad that you're interested in pediatric rheumatology and all the rare diseases need a little boost to their voice. So, thank you for doing that for them.

Vincent: Thank you for helping us raise awareness of our conditions.

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 e-newsletters on the site.