**The Rise of Big Data Registries in Rheumatology – Part 2**

**Transcript**

**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, much more. So let's dive in.

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**Meghna:** In part 1 of the series, we got insight into some of the registries in rheumatology, including ArthritisPower, CorEvitas, and the [American College of Rheumatology] (ACR)'s RISE Registry. In the second part of this series, we're getting updates from 2 more data registries in rheumatology.

My first guest today is a pediatric rheumatologist and a researcher who is affiliated with the CARRA registry, the Childhood Arthritis and Rheumatology Research Alliance Registry. We're speaking with Dr Yukiko Kimura, a co-principal investigator of CARRA and a professor of pediatrics at Hackensack Meridian School of Medicine, New Jersey. Hello and welcome, Dr Kimura.

**Dr Kimura:** Thank you so much. So happy to be here.

**Meghna:** First of all, congratulations on the incredible work on the CARRA registry since its inception in 2015. The registry has definitely come a long way and has been a pioneer since then in informing better research and therapeutic options in pediatric rheumatology.

**Dr Kimura:** Absolutely. We have really come a long way from when we started the registry in 2015. Actually, over the last few years, we have built up the registry so that we now have [more than] 11,000 patients enrolled in the registry and it's still growing, and we plan to follow-[up with] each patient for at least 10 years. We also have increased the number of sites participating in the registry to 76 sites, with 62 of them having the ability to collect biosamples, and so it's really producing tremendous amounts of data and information.

**Meghna:** I had a chance to sit in on some sessions at the CARRA 2021 conference last month. It was an interesting format with intriguing sessions, but just getting to the point, could you take us through some of the work stemming from CARRA over the last few years?

**Dr Kimura:** The CARRA organization itself has grown tremendously since it started with 20 investigators in 2002. Currently, [it] involves more than 90% of all the pediatric rheumatologists in North America, with [more than] 600 members and more than 140 sites. We have a strategic partnership with the Arthritis Foundation since 2015, and we're doing tremendous amounts of work with different disease-specific research committees, as

well as research committees that go across diseases, from studying, problems like reproductive health in our patients, transition, mental health, etc, [and] also, dozens of work groups doing work on specific topics within diseases. So, we have really come a long way, developed many tools for studying our patients, which, hold at the center of it, of course, the CARRA registry.

**Meghna:** The registry has enrolled more than 10,000 pediatric patients, you know, with various rheumatic conditions, including juvenile idiopathic arthritis and dermatomyositis, lupus and scleroderma. In fact, prior to our conversation, I was looking at the paper by Dr Beukelman et al, published in *Pediatric Rheumatology Online* in 2015, about the characteristics of patients with juvenile idiopathic arthritis enrolled in the first 12 months of the registry. But there has been such an evolution of the registry since this study. Are there plans to expand into the other pediatric rheumatologic disease states as well, Dr. Kimura?

**Dr Kimura:** Well, of course we would love to enroll and follow-[up with] every patient that is treated at our centers – that would be our goal, and that would include all the diseases. For example, we would love to add autoinflammatory diseases and chronic recurrent multifocal osteomyelitis. Both disease states have a lot of interest, as well as vasculitis, to start with. But adding more diseases and more patients does cost money, so we have to find ways to fund these efforts. So, that's what we're working on now. Also, to find ways to make it less expensive to add diseases by, for example, maybe adding them as parallel databases that link to the registry using patients' global IDs.

**Meghna:** That's wonderful. You know, just talking a little bit about 1 of the aims, or the potential aims, of the CARRA registry, to follow-up with patients' long-term, thus increasing the availability of longitudinal data. I'd imagine this can be quite a challenge with pediatric patients, right, especially among those on the cusp of transitioning into adult rheumatology care. How can this aspect of data collection be handled or how is it currently being addressed?

**Dr Kimura:** Our long-term follow-up program is an incredibly important aspect of the registry and one that allows us to achieve 1 of our major objectives, which is to be able to assess the long-term impacts of these diseases and of the medications used to treat them. The program uses a call center at the Duke Clinical Research Institute, which has a very high success rate in reaching participants. But this is the first time that they've had to try to reach participants who are of a younger generation, say, than they're used to, and that it's been interesting that it's been much more challenging to reach young people and young adults who don't have landlines or who don't answer their phones. So, we're developing ways now to reach our participants, using text and emailing, and also developing a survey instead of having patients stay on the phone to answer questions, which I think they appreciate.

I think most importantly, we realize that we really have to really engage our patients while they're still seeing the pediatric rheumatologists so that they understand what the registry

is and why they're participating in it and why they're going to be asked questions about how they're feeling and how they're doing and if they're having any side effects from the medications that they're taking after they graduate from the pediatric rheumatologist.

**Meghna:** And, you know, it's important to note just the barriers involved in registering pediatric patients in clinical trials and research studies, like you mentioned. So, this is definitely a great initiative at the CARRA registry. I can't wait to see its impact on improving patient management and care in the future.

**Dr Kimura:** Yes, absolutely. Enrolling patients, any patient, in a clinical trial is challenging, but it's especially true in pediatric rheumatology because the diseases themselves are rare and, of course, they involve children. I think that especially for randomized clinical trials, this is particularly problematic, especially when placebo-controlled trials are done. In the past, in pediatric rheumatology, we've done randomized withdrawal trials. But, as time went on - and actually that's how Enbrel got approved for use in children – [w]e came to realize that because everyone is exposed to the drug, there are no really true untreated control patients, right? Also, we didn't know what happened to the patients who didn't respond because they were eliminated from the trial itself. And now, these days, very few patients want to participate in the placebo-controlled randomized trials because there are so many other treatment options that are already available to them, out there.

Using an observational study platform, like the registry, to do comparative effectiveness studies is something that CARRA wants to do more of, and what that means is that we enroll patients in the registry, and patients, [p]arents, and the physician [decide] which consensus treatment plan or CTP they want to use to treat the patient, and then they get followed [up with] in an observational way through the registry. If it's done in a standardized way and there [are] data collected that is standardized, we're able to really learn a lot about how these treatments compare.

The first actually large-scale study to do this, which is called StopJIA, was completed, and the primary results are going to be published within the next few weeks. So, we're really excited to see this happen, because we think this is a model that could be used that's much easier to enroll than in a standardized, randomized controlled study.

**Meghna:** So, just a sneak in a quick question here, Dr Kimura. You had mentioned to me earlier about the CARRA registry aiming to serve as a platform to enable research studies in pediatric rheumatology.

**Dr Kimura:** The registry really is being used as a platform for doing multiple kinds of research studies, not only for just, you know, observational and natural history studies of our diseases, but to be able to do comparative effectiveness research, pragmatic trials, translational studies, using biospecimens that we collect on registry participants, as well as randomized clinical trials. So, all of these types of studies are using the registry. Really, data collection is the backbone on which these studies are built.

**Meghna:** Investigators at CARRA and the Duke Clinical Research Institute are working to include in the registry cases of [COVID-19] among enrolled patients. Dr Kimura, can you tell us more about this project and what has been learned so far?

**Dr Kimura:** Sure. So obviously, we are all interested in how our patients do if they develop [COVID-19]. So it is a reportable adverse event in a CARRA registry. Any registry participant who develops [COVID-19] infection will be reported and recorded as an event of special interest. So far, 180 of these events have been reported since the pandemic began.

We also collaborate, though, with the Global Rheumatology [COVID-19] registry and so we've set up a parallel registry for pediatric patients who are not registry participants who developed [COVID-19] and their rheumatologist wants to report them. So, we have, I believe, about 70 patients reported in the registry so far in the US and Canada; and there are also parallel registries going on in Europe and in other countries as well that will eventually report to the Global Rheumatology [COVID-19] registry.

**Meghna:** Oh, interesting! Lastly, Dr Kimura, what's next for the registry? Anything exciting in the pipeline that you can share with us?

**Dr Kimura:** Sure. So, patient engagement has always been very important to CARRA and over the last few years, we've really involved patients and parents in almost every study that we've done. In terms of study, helping with designing the study, asking the questions that they feel are important, and also helping us in terms of when we have enrollment barriers, when we have trouble collecting biospecimens on patients. That is something that we want to continue to do in a really strategic way.

One of the projects that we're going to be launching soon is that we're going to be developing patient-facing apps to collect patient-reported outcomes and other information from patients on participating in the registry, in-between visits to the registry or even to the site for their regular checkups. We also are going to be using this to hopefully begin studies that are enrolling patients directly and not having to do it at a clinical site, for example.

We are also going to be using platforms that will allow remote consenting and other remote activities because, as you know, because of [COVID-19], a lot of processes have become remote. These are some exciting initiatives that we're going to be starting very soon.

**Meghna:** This has been an excellent opportunity for me and our listeners to learn more about CARRA and the incredible work being done. Thank you, Dr Kimura, for your time today.

**Dr Kimura:** Thank you. It was a pleasure speaking to you.

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**Meghna:** My final guest in this series is Dr Pedro Machado, associate professor and consultant in rheumatology and neuromuscular diseases at the University College London, and the chair of the [European Alliance of Associations for Rheumatology] (EULAR) Standing Committee on Epidemiology and Health Services Research and the COVID-19 Global [Rheumatology] Alliance [(GRA)] Steering Committee.

Thank you so much for joining me today from London, Dr Machado. I appreciate that we were able to figure out a convenient time for both of us, despite the time difference!

**Dr Machado:** Well, thank you for inviting me. It's a real pleasure to be here today.

**Meghna:** I wanted to congratulate you and your entire team at the COVID-19 Global Rheum Alliance for a well-deserved and successful year. I saw that you celebrated the 1-year anniversary recently.

**Dr Machado:** Indeed, and it was a very exciting moment. It's been a very strange, but also very rewarding year in terms of the data we collected so far.

**Meghna:** Absolutely. I even saw on the website today that data from more than 15,000 global cases of COVID-19 have been entered into the registry, and that's amazing.

**Dr Machado:** Indeed. It's an amazing achievement and we have to thank the entire rheumatology community for it. The level of engagement has been amazing and without them, we wouldn't have been able to reach these numbers.

**Meghna:** Yeah. [J]ust thinking back to last year, very little was known about SARS-CoV-2 and [COVID-19] when the registry was initiated. I mean, in all honesty, we know just a little bit more about the virus and disease even today, but with lots of unanswered questions still remaining. But tell us, Dr Machado, how has your overall experience been so far? How did you come to be associated with this registry, and also, what were the initial objectives in 2020?

**Dr Machado:** Well, what prompted the creation of the registry was the concern that the outcome of COVID-19 could be worse in patients with rheumatic diseases, right? And that's how I got involved with the Global Rheumatology Alliance. Because of legal issues, it was important to have a data collection system in Europe because of data protection issues that was different from the one that is being used in the US, and, in fact, in the rest of the world. Then there was communication between the Global Rheumatology Alliance and the European League Against Rheumatism, so EULAR. This is, in fact, how I got involved with the registry initially because I helped set up the European branch of the registry and then I also became a member of the GRA steering committee.

**Meghna:** Amazing. You know, we're all so grateful to the physicians and organizations that have collaborated and continue to work towards achieving the goals of the registry to improve outcomes for patients with [COVID-19] and rheumatologic disease. Dr Machado, can you speak to the importance of accuracy and precision of these collected data for clinical practices and how it can potentially help rheumatologists, or rather, how has it

already made an impact in terms of informed decisions during patient care and management in the pandemic? Has there been any feedback or real-world evidence?

**Dr Machado:** So, we started in late March 2020, and the data, they're entered voluntarily by rheumatologists or by other health care professionals working with rheumatologists. There is only 1 single inclusion criteria, which is the patients need to have a pre-existing rheumatic disease and having being infected with SARS-CoV-2. As a cross-sectional registry, or a case-reporting registry, we can explore factors associated with certain [COVID-19] outcomes, and obviously, the outcomes of interest are severe outcomes, such as hospitalization or [intensive care unit] (ICU) admission or death.

However, these are [only] associations, because this is an observational study, and we need to be cautious about what we call causal interpretation of the results. Some of the factors that can be studied are, for example, demographic factors, clinical factors, the underlying rheumatic disease diagnoses, and importantly, the antirheumatic medications that the patients are taking. Now, so far, we have been able to study factors associated with hospitalization and death in a variety of patients with rheumatic disease, and these results have already had practical implications.

What we've not been able to do, mainly because of limitations in the number of patients, is to look at every [individual's] rheumatic disease, obviously. So, we were able to look at some of the most prevalent ones, but for the more rare disease we have not been able to do that so far.

The other thing [that] I think it's important to bear in mind is that we don't have a population-based comparator, so we cannot make comparisons between, for example, [patients with] rheumatic disease with and without [COVID-19].

Also, there's a bit of selection bias because cases that are more severe are always more likely to come to the attention of the rheumatologists, and therefore, they're also more likely to be reported.

**Meghna:** But when we're talking of limitations, I'm sure none of this was easy. Putting together something of this magnitude in the midst of a global pandemic. What were some of the initial barriers faced with respect to the registry and [h]ow were they overcome?

**Dr Machado:** One of the major barriers is always to create a registry, a survey, [which] would be feasible to complete in practice. Finding this balance between what is easy to do and feasible to do in clinical practice and comprehensive enough to give us the information that we needed is sometimes not easy. I think we [were] quite successful, in fact, and I think we created a quick and easy survey while knowingly sacrificing some of the data that would allow us to do more complex analyses, in particular, longitudinal analysis. But there needs to be a balance there, so I think 1 of the important barriers was actually to find that balance.

Then, the uptake of the registry itself; you never know what the level of uptake is going to be. I think we did a very good job in terms of communicating it to the wider rheumatology community. I think the partnerships that have been established, they were very successful.

Maybe a third one that I should probably mention, we need to be very aware of the general data protection regulations, and they differ between continents. That's, in fact, what happened with the European Union, and that's why we needed to, we had to set up a different parallel registry that is based in Manchester in UK while the global one is based in San Francisco, California.

**Meghna:** You know, I have to tell you, from what we see, the achievement with the registry has, of course, has been fantastic, and importantly, the urgency in the response of the rheumatology community to the pandemic has been inspirational, to say the least.

Now there's so much news coming out of the registry. I saw that, now, patients with rheumatic disease can report their COVID-19 vaccination experience. But what do you believe has been the most successful aspect of the registry yet? And can you provide some of the latest updates, Dr Machado?

**Dr Machado:** I think the most successful aspect has definitely being the high level of engagement and support from the rheumatology community. You know, it's just been unbelievable. We now have more than 16,000 cases reported to the registry, and that's actually quite unique, that level of support, in such a short period of time.

In terms of latest updates, we did publish a paper in January, which I think was a very important paper. So, in that paper, we reported the outcome of almost 4000 cases of patients with rheumatic diseases and COVID-19. And obviously now, we're analyzing the rest of the dataset. But, in that paper, which was published in *Annals of the Rheumatic Diseases*, we found several things that have practical implications. One of them was that older age and male gender was associated with COVID-19-related death. So, for example, of those who died, [more than] two-thirds are [older than] 65 [years], and then, the risk [for] dying was even higher people [older than] 75 [years], and also, in men compared [with] women. This is, in fact, very similar to what has been observed in the general population. So, I think the message here is that our patients are not that different from the general population.

We also found that comorbidities were more common in people who died from COVID-19, and again, this is in line with the data from the general population. And, for example, the presence of chronic lung disease or having cardiovascular disease combined with hypertension was associated with COVID-19-related death, as was chronic kidney disease, but all that only in the subset of patients with connective tissue disorders and vasculitis.

**Meghna:** Yeah, [those are] all very compelling data. I was also talking with Dr Kimura of CARRA previously who mentioned the collaboration with the COVID-19 Global [Rheumatology] Alliance on pediatric data, and that's another intriguing area of research.

**Dr Machado:** Yeah, we are collecting data from pediatric patients and we expect to publish [those] data soon. There's going to be, in fact, an abstract that is going to be presented at EULAR [2021 Virtual Congress]. Obviously, in children, they tend to have a much more benign course of the disease, but it's important to see if that is also the case in patients with rheumatic diseases because of the underlying immune dysfunction and the medications that they take. In fact, that does seem to be the case and some of [those] data will be presented at [the] EULAR [meeting] in June.

**Meghna:** Looking forward to that. Finally, what can we look forward to next from the registry?

**Dr Machado:** Well, as I explained, [w]e were really able to study a significant number of factors that are associated with severe COVID-19.

In fact, 1 of them that I didn't mention, but I think it's really important, is that in that paper from January, we also found that patients with higher disease activity were more likely to die from COVID-19. To me, that's a really important finding because it highlights the importance of controlling disease, of treating our patients, including in the context of a viral pandemic. With increasing numbers, we will be able to do this in more specific populations, especially more rare diseases, such as vasculitis or myositis, and we will also be able to look at less commonly used drugs, such as some of the immunosuppressive medications. But that can only be done with larger numbers.

So, in summary, I think the next step is to look at more granular details of our population and to obtain more granular insights into the risk factors for COVID-19 in patients with rheumatic diseases.

**Meghna:** Dr Machado, I speak on behalf of everyone when I say thank you and your team for the great work with the registry, and I will be sure to keep my eye out for, all the exciting stuff coming up, and hopefully some positive news on the [COVID-19] front as well.

**Dr Machado:** Thank you, and thank you for the invitation again.

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**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.