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Unmet Needs in SLE: The Challenge of Achieving Sustained Disease Control

Announcer:
You're listening to *Living Rheum* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. This is a non-certified educational series produced and controlled by ReachMD. And now, here's your host, Dr. Steve Jackson.

Dr. Jackson:
Welcome to *Living Rheum* on ReachMD. I'm Dr. Steve Jackson, and joining me to discuss how we can address unmet needs in systemic lupus erythematosus, or SLE, treatment is Dr. Maria Dall'Era. She's the Chief of the Division of Rheumatology, Jean S. Engelman Distinguished Professor of Rheumatology, and the Director of the Lupus Clinic and Rheumatology Clinical Research Center in the Department of Medicine at the University of California, San Francisco.

Dr. Dall'Era, thanks for being here today.

Dr. Dall'Era:
Thank you so much for having me. It's great to be here for this discussion today.

Dr. Jackson:
Current SLE therapies have given us the ability to modulate immune activity and reduce disease activity for many patients. When we look at the underlying B-cell and autoantibody-mediated pathophysiology of SLE, how would you describe where SLE management stands today?

Dr. Dall'Era:
We're living in a very exciting time in terms of the management of SLE. For decades, we depended on non-specific immunosuppressive, anti-proliferative therapies like mycophenolate, azathioprine, methotrexate, the old alkylating agent cyclophosphamide, and, of course, glucocorticoids, which are the most potent anti-inflammatories that we have available to us. We relied on those medications for decades, but now we are in a time where we are using targeted therapies, often in addition to some of the conventional therapies that I mentioned.

But these targeted therapies are special because they impact the immune system in very specific ways. And I like to think about the pathogenesis of lupus from a 30,000-foot view, having two major components. One is activation of the innate component of the immune system, and the prototypic cytokine that we often talk about on the innate immune system side is type I interferon. And then on the other side, we have the adaptive immune system, and we're all familiar with that. We're familiar with autoantibodies, B-cell hyperactivation, and loss of tolerance in the B-cell and T-cell compartment. But in lupus, we have both sides, with both the innate and the adaptive immune system playing a role, as well as interrelated pathways between those two components. And we have a pipeline full of targeted therapies.

Dr. Jackson:
So let's take a closer look at how we approach disease control in practice. Treat to target has become central in SLE, and what do targets like DORIS remission scores and LLDAS represent, and what does achieving them entail?

Dr. Dall'Era:
We wrote these into the American College of Rheumatology guideline for the treatment of SLE. We specifically called out treat to target and aiming for remission or low disease activity. And the two most commonly used indices that you will see showing up in clinical trials —we're also trying to extrapolate them to clinical practice, although it's a little bit more challenging, but we're trying to do that—are

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DORIS remission, which is very stringent with a clinical SLEDAI of zero, which means no clinical disease activity, but you can have a positive serology. It's okay to have a positive anti-DNA, and it's okay to have a low complement, but just no clinical disease activity. And importantly, the prednisone dose has to be less than or equal to five milligrams a day.

A less stringent target is what we call LLDAS. And with that, the SLEDAI-2K has to be less than or equal to four, and the prednisone dose can be up to 7.5. And so we aim for remission; that's really what we should all be aiming for. But, if we're not able to get there with our current therapies available to us, another target is LLDAS, which is a low disease activity. Again, it's not as good as DORIS. Importantly, the literature has shown us now multiple studies that time in DORIS remission or time in LLDAS is associated with better outcomes, less disease damage accrual, fewer disease flares, lower mortality, all of those things. So these are endpoints that are clinically meaningful to our patients and improve outcomes of the disease.

Dr. Jackson:
And in your experience, how attainable and sustainable are those targets, particularly given how patients can respond so differently to individual treatments?

Dr. Dall'Era:
I think we're doing a lot better. And so when you look at the literature now, people have looked at this, trying to understand how we're doing in achieving these targets with our targeted therapies. So, for instance, drugs like anifrolumab or belimumab versus our conventional therapies, and we know from a variety of analyses that we are doing better. We are more likely to achieve those targets with these newer therapies. However, we are still not achieving these targets at the rates that we want. We're still way under 50 percent of patients achieving these targets. These are data from the randomized controlled trials and post-hoc analyses of the randomized controlled trials.

I would sum it up by saying that we are doing a lot better. We've made huge progress, but we still have significant unmet need in achieving these low levels of disease activity, and that's where I think we all are looking to the future. We're looking at additional newer targeted therapies and different classes of medications. How do we use maybe the medications that we have in better combinations?

And then you alluded to something very important when you said "individual responses." I think what we're all trying to understand better is which immunologic pathway is operating in which of our patients. We don't have biomarkers yet that tell me if my patient in front of me is going to respond better to a type I interferon-blocking therapy versus an anti-BAFF therapy versus another B-cell targeted therapy. We don't know that yet, but we will get there, and that research is being done.

I think all these things have to converge over time for us to be able to do better and have the best response rates that we would hope for.

Dr. Jackson:
For those just joining us, this is *Living Rheum* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Maria Dall'Era about the challenge of achieving sustained disease control in systemic lupus erythematosus.

Now, Dr. Dall'Era, maintaining disease control can mean staying on multiple therapies over time. What challenges can that create for patients, especially for quality of life and adherence?

Dr. Dall'Era:
I see this every day in my own clinical practice taking care of patients living with lupus. But I can also speak from the vantage point of my experience as one of the core members of the American College of Rheumatology guidelines for the treatment of SLE, in which we had a patient panel. Our patients described for us the challenges they faced with the medications that we prescribe, and I vividly can still hear many of their voices. And we actually published the patient voice as well. It's very challenging, and they talk about the side effects.

I'm going to give you some examples. With mycophenolate, patients talked about the GI distress. One of them said, "Food is very important culturally to me and my family, and I can't eat the foods that I want to eat because of the stomach upset with that medication." Challenges with the side effects of prednisone. Many side effects of prednisone. Looking at all of these pills every single day. Patients talked about just feeling the sense of overwhelm trying to manage multiple pills. Some of them are taken on an empty stomach, some are not, and some are in the evening, some in the morning. "How do I do this? I'm trying to go to school." "I'm taking care of kids." All of those things came up with our patient panel, and they expressed all of these concerns with the medications, and it was very enlightening for all of us to learn from our patients living with lupus.

I also think we understand now that we have these targets. We talked about things like DORIS remission and lupus low disease activity state, also known as LLDAS. But for our patients, there are so many other things that they care about that are important to them that we don't address, like fatigue, pain, and cognitive dysfunction. And we often hear from our patients that our current medications don't address those other symptoms, and those symptoms have a dramatic impact on their quality of life.

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And so I think all of this is to say that we need to continue to do better. We've come a long way, but we now need to take it to the next level and try to address all these other concerns.

Dr. Jackson:
So when a patient's disease remains active over time despite treatment, what are the potential longer-term consequences, and how do factors like glucocorticoid exposure and organ damage accrual come into play?

Dr. Dall'Era:
What we've learned over the past few years is that organ damage, which is an irreversible fibrotic tissue disruption, or architectural disruption of tissue, happens earlier than we thought. We now know that because people have studied this in cohorts we call "inception cohorts," or patients with newly diagnosed lupus following them over time. Damage happens really early, and we think that the two major mechanisms of damage are inflammatory disease activity that's not being treated, and the second major mechanism in lupus, honestly, are the glucocorticoids, which have a significant amount of damage over time. And they both converge.

And so you can imagine that a patient who has a flare has increased disease activity and increased inflammation, and that's going to lead to scar fibrosis damage. At the same time, they're getting higher doses of prednisone to treat the flare, and that prednisone is going to lead to damage. So it's very challenging. We see it early. We don't yet have a way in 2026 to reverse fibrosis; we don't have a way to do that. So we have to prevent it from happening to the best of our ability. We know it happens early, and so we have to treat early.

And the other thing that's top of mind is the major issue of cardiovascular damage. We've known for decades that patients living with lupus have an increased risk of atherosclerotic cardiovascular disease and mortality from that. And we know that most of the immunologic pathways that are operative in atherosclerosis are also operative in lupus. So when people have smoldering lupus disease activity, which we might not even be able to detect clinically, they can be having ongoing cardiovascular damage. And so we have to figure out a way to measure that better.

But it just brings home the fact that we just need to do a better job, I think, recognizing disease activity, getting better tools to do that, treating proactively early with effective therapies that shut down these immune pathways, and trying to use the lowest dose of glucocorticoids that we can get away with, preferably zero. But sometimes we still have to use it as a bridge, particularly for organ-threatening diseases like lupus nephritis. We know that. But the lowest dose for the shortest duration of time, and that's what we wrote into our guideline as well, and the goal glucocorticoid dose now should actually be zero. That's an important difference as well in the guideline.

Dr. Jackson:
Now, all of this raises the question of whether we can aim for a different kind of long-term outcome. What should we know about drug-free remission as an emerging research goal in SLE?

Dr. Dall'Era:
I think this is where the future is headed, and we've all been very interested. Can we somehow change the immune system? Some people call it reset, and some people call it reboot. Different terms that are not yet clearly defined, but we're in the process of trying to define these terms better. But is there a way to basically get the immune system back to where it was before a patient had lupus, before a patient had all this immune dysregulation? And can we do that in such a way that patients can come off all of these therapies that are giving them side effects? We call that "drug-free remission." Maybe they're on hydroxychloroquine only. Maybe they're not even on that; we don't know. But that is, I think, a major promise for our patients: can we actually get to that point where we're able to do that? And that, I think, is the next frontier, and there are many studies ongoing trying to figure this out.

Dr. Jackson:
As we come to the end of today's program, I want to thank my guest, Dr. Maria Dall'Era, for joining me to share her perspective on long-term disease control in patients with SLE. Dr. Dall'Era, it was great speaking with you today.

Dr. Dall'Era:
Thanks for having me.

Announcer:
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