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## Examining the Role of Biologics in the Treatment of Lupus

### Announcer:

You're listening to *Living Rheum* on ReachMD. This episode is sponsored by GSK. Here's your host, Dr. Jacob Sands.

### Dr. Sands:

Welcome to *Living Rheum* on ReachMD. I'm Dr. Jacob Sands, and here with me today to examine the role of biologics in the treatment of lupus is Dr. Daniel Arkfeld. Dr. Arkfeld is Professor of Clinical Medicine and Director of Continuing Medical Education at the Keck School of Medicine of USC. Dr. Arkfeld, welcome to the program.

### Dr. Arkfeld:

Well, thank you. Thank you for inviting me.

### Dr. Sands:

To start us off, Dr. Arkfeld, can you give us a brief overview of the pathophysiology and clinical course of lupus?

### Dr. Arkfeld:

The pathophysiology relates really to the innate and adaptive immune system. The adaptive immune system produces antibodies, B cell and T cells; both are overproduced. Antibodies trigger a variety of autoimmune disorders - including lupus. Lupus seems to also involve the innate system as well; toll receptors seem to be very important. A lot of other factors are coming out, and there's also been about a hundred different genetic susceptibility genes that are being researched as potential factors. It probably leads to many antibody productions; ANA should universally almost always be positive in lupus. The double-stranded DNA up to 70% antibody, 30% Smith antibodies, and you get a lot of like the Sjogren's antibodies, 20 to 30% positivity. So, these antibodies are produced in excess and when they trigger disease for whatever factors, which lack of regulation, too much inflammation, all areas are being looked into quite a bit. And what happens with these antibodies is they target different parts of the body. I always try to separate people that have more peripheral lupus with joint pains and fatigue and rashes versus those that have internal organ involvement, more kidney, lung, brain inflammation.

### Dr. Sands:

So with that background in mind, how do we typically treat lupus, and what outcomes can we expect from standard therapies?

### Dr. Arkfeld:

So lupus has really evolved from controlling their symptoms to really what we're getting into rheumatology what I like to call treat-to-target initially in rheumatoid arthritis and then gout and other disorders. And now it's really being applied to lupus. And the goal is really not to make people feel better and more comfortable, but really let's prevent organ damage in the long run. But then we get into treatment, I think it all starts with hydroxychloroquine; 5 mg/kg is the latest dose recommendation. And I think hydroxychloroquine, which targets innate systems toll receptor 7 and 9, is really a backbone of lupus and probably most lupus patients, unless they have an allergic reaction or an issue with the eyes or something, probably should be on hydroxychloroquine therapy. Then it gets into individual problems; more joint pains, we may use a little more methotrexate. Unfortunately, a lot of times these are young females where methotrexate can cause birth defects and so we really don't use that in that population. Gets into azathioprine, another drug that we commonly use quite a bit. That has a risk of having lymphoma; also if you don't check a T-BMP before it can actually drop their counts quite a bit. And then I think there's a whole group of refractory lupus patients where nothing works where we use a lot of other agents as well. And I think biologics was the topic of this conversation; start early but over time there's spots where we also use them.

### Dr. Sands:

Now you've mentioned biologics, so let's dive into that a little bit more. Can you tell us about this class of drugs and what's currently available for lupus?

**Dr. Arkfeld:**

Biologics are used in many specialties. In rheumatology, they really started in the 90s with the advent of TNF blockers for rheumatoid arthritis. But biologics have come out for lupus as well with two agents currently FDA-approved: belimumab and anifrolumab. We can talk about them in a few details. Belimumab is an anti-BAFF agent, which it affects B cells. And anifrolumab is a type 1 interferon receptor blocker. So both these have two FDA-approved indications. Belimumab has been out for many years, recently got approval for nephritis, which has been very key in being able to have that class 3, 4, or 5 lupus nephritis therapy. As such, it's very effective for joint pains, fatigue, rashes, and other factors in lupus. Anifrolumab seems to be very effective, especially for fatigue, energy, not as much for organ involvement at this point. Future studies, we'll see how that goes.

**Dr. Sands:**

For those just tuning in, you're listening to *Living Rheum* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Daniel Arkfeld about the role of biologics in the treatment of lupus.

So Dr. Arkfeld, now that we've gone through some of the biologics that are available, how do you determine whether or not this is the right option for your patient and what are some of the specific things that you focus on in your consideration?

**Dr. Arkfeld:**

Well, I think the key thing in lupus is also following a patient over the long-term. It's not like in rheumatology we can have the opportunity to see people every month, every three months, every six months. A patient doing well with lupus, I typically see them every three to four months. Some people say it can go every six months, but I think if you just really want to measure and catch a lupus flare, seeing them in between is good. And usually, we're monitoring the blood tests as well as doing the history and physical examination. In the blood tests, we look for complements dropping; the C3 and C4 levels sometimes drop with a flare. And with that you do have a rise in the double-stranded DNA, all of them most worrisome for organ involvement when that happens and that's something we definitely keep an eye on. The white counts can also drop and get a little more leukopenic, and occasionally, hemolytic anemia can occur. We also monitor the complements double-stranded DNA. We'll also do a CBC to catch those factors and also a chemistry panel because we really want to pick up nephritis occurring earlier. And lastly would be urinalysis and specifically we're really monitoring urine, ratios for protein quite a bit, trying to get that below 0.5 if at all possible. So we monitor or follow the patients; typically, they'll have symptoms occurring before a flare. The only ones that don't really have symptoms, which sometimes can be kidney or hematological involvement, that's why I like to do the blood tests as well. But typically, a lupus patient will flare in multiple ways: joint pains, rashes, more Raynaud's phenomenon, malar rash, oral ulcers. So we have to put our detective hat on and really monitor for flares in these patients.

**Dr. Sands:**

And once you select a biologic, can you talk a bit more about these side effects that you're looking for and how you'd manage those?

**Dr. Arkfeld:**

Side effects really depend on the biologic agent. Most of them are well-tolerated and I separate out the efficacy like getting them to remission and near remission or really getting the benefit from the biologic that we're looking for and then dealing with side effects. When you mess with the immune system, the biggest side effects would be infections, which may be shingles infections, which are high with certain agents, maybe other bacterial infections or viral infections, currently dealing with coronavirus issues and we worry about that in these patients that they may be more immunosuppressed, possibly needing monoclonal antibodies and/or the new oral agents that'll be coming out. And so infection is a big risk with that, and then each specific one whether we're blocking alpha 1 interferon, we're blocking B cells, T cells, they all have their own unique set of side effects that we need to monitor for. But the key is really I think infections that we worry about. And then certain vaccines, you know, like live vaccines which shouldn't be used. Some vaccines may not take as well on these things, so we adjust medicines for them as well.

**Dr. Sands:**

So Dr. Arkfeld, based on your experience, do the outcomes associated with biologic therapy outweigh the risk of the side effects you just mentioned?

**Dr. Arkfeld:**

Yes, I mean obviously risk involves an individual and risk can occur with a lot of therapies; biologic therapies block the immune system. The immune system can trigger infections when it's blocked and whether it's a viral infection, shingles exacerbation, bacterial infection, or other infections. That's probably the main thing that we do worry about. The immune system does also coordinate a lot of other factors and such and so many other things are out there. But in general, the risk of the disease with organ damage, especially with the kidney. 50% of lupus patients will develop kidney disease in the course of their disorder and if they lose nephrons and they end up as

they get older going on dialysis or renal transplant, we're really trying to avoid that. Biologics are amazing in helping us reduce that risk and I think it really is necessary at this time. So this is all includes a discussion with the patient, the risk/benefit, focusing in on the risk, but also on the potential benefits and coming to an agreed upon decision on which route we should go, whether it be using drug X, Y, or Z or biologic A or B out there and really custom tailoring a treatment course for each patient.

**Dr. Sands:**

Now we're almost out of time, but before we close, Dr. Arkfeld, any other final take-aways or forward-looking comments you'd like to make for our audience?

**Dr. Arkfeld:**

I think the rheumatology community, they start seeing these new recommendations, they're going to realize that wow, we're being way more aggressive with lupus, we're really targeting, trying to eliminate as much as we can this disorder. We're hopeful; improving our outcomes, preventing kidney damage, loss of nephrons is our goal, preventing dialysis in the long run if at all possible whether it's lung involvement, heart, pericarditis, whatever. Each treatment is approached differently. It makes rheumatology a fascinating field to participate in, but I think it's also one that you definitely have to be looking at the whole from head-to-toe because it can affect anywhere in their body and not to just fixate on the blood or the kidneys or whatever with these patients. Be open-minded, work with them, see them, have the patients let us know when they think they're flaring or they're having symptoms, and see the patients and reassess the best endpoint. So I think it's really the physician/patient relationship for treatment for risk and benefit discussions, but also to make sure that they're doing the right thing as much as possible is really our goal in rheumatology.

**Dr. Sands:**

Well with those final thoughts in mind, I want to thank my guest, Dr. Daniel Arkfeld, for sharing his perspective on the role of biologics in the treatment of lupus. Dr. Arkfeld, wonderful speaking with you today.

**Dr. Arkfeld:**

Oh, well thank you very much for this opportunity.

**Announcer:**

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