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Managing Lupus Nephritis: Multidisciplinary Insights on Recent Guideline Updates

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Managing Lupus Nephritis: Multidisciplinary Insights on Recent Guideline Updates," is sponsored by Aurinia Pharmaceuticals.

Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD, and I'm Dr. Charles Turck. Here with me today to discuss the recent guideline updates for the management of lupus nephritis, are doctors Maria Dall'Era and Tina Kochar. Dr. Dall'Era is Professor and Chief of Rheumatology at the University of California San Francisco. She's the Director of the Rheumatology Clinical Research Center in the UCSF Lupus Clinic.

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

Dr. Dall'Era:
Thank you very much. It's a pleasure to be with you here today, and I'm looking forward to our discussion.

Dr. Turck:
Dr. Kochar is a Nephrologist and an Associate Professor of Internal Medicine and Director of Glomerular Diseases Clinic at University of Texas Medical Branch, Galveston. Dr. Kochar, it's great to have you with us as well.

Dr. Kochar:
Pleasure to be here and I look forward to this discussion with Dr. Dall'Era.

Dr. Turck:
Now, before we dive into our discussion, let's take a moment to review the indication in boxed warnings for Lupkynis, which will be referred to as voclosporin throughout this program.

Announcer:
INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

LUPKYNIS is indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN).

***Limitations of Use**:* Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

CONTRAINDICATIONS: LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because of the increased risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to increasing doses and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants, including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections which lead to serious, including fatal outcomes.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), may cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity. Monitor eGFR regularly.

Dr. Turck:
To start us off, Dr. Dall'Era, could you give us a brief overview of lupus nephritis in patients with SLE?

Dr. Dall'Era:
Lupus nephritis is the most common of the organ-threatening manifestations of SLE, and it's associated with significant morbidity and high mortality. Just to give you some data, it's estimated that about 30% of patients who are diagnosed with a class 3 or class 4 lupus nephritis will progress to end-stage kidney disease within 10 years of diagnosis. And this is significant when you think about the age of diagnosis of the majority of patients with SLE and lupus nephritis, where there tends to be an increased incidence in patients of childbearing age. These are young women, predominantly, who are diagnosed and have this significant risk of end-stage kidney disease early in their disease course.

It's also important to remember that lupus nephritis itself is a risk factor for increased mortality as well as atherosclerotic cardiovascular disease. And remember that reduced kidney function and proteinuria are independent risk factors for coronary artery disease. For all of these reasons, it's very important that we diagnose patients early with lupus nephritis and treat it appropriately, so that we can prevent these poor long-term outcomes.

Dr. Turck:
And turning to you now, Dr. Kochar, can you tell us about the different factors that influence the prognosis of patients with lupus nephritis?

Dr. Kochar:
Absolutely. So there are several factors that play an important role. The most important one being level of proteinuria. We know the level of proteinuria increases risk of poor outcomes, even in patients with preserved kidney function. Some of the other factors include ethnicity. Our minority patients, African Americans, Hispanics, and Asians have more aggressive disease with worse outcomes. Also, response to treatment plays a role in the prognosis. The faster these patients go into remission, the better long-term kidney survival they have.

Dr. Turck:
Thank you both for that key background information. Now, if we come back to you, Dr. Dall'Era, what's your typical approach to screening for lupus nephritis in patients with SLE?

Dr. Dall'Era:
Thank you for this question. It's very important. Once a patient is diagnosed with SLE, it is critical that we perform surveillance or screening for the onset of lupus nephritis. And what this typically looks like in our clinic is once a patient is diagnosed with SLE and we're following them in the clinic, it's important, at typically 3-month intervals, to screen them for the onset of lupus nephritis. So what does that mean? That means sending a variety of laboratory tests, including serum creatinine, EGFR, as well as urinary parameters such as a urine protein to creatinine ratio, a urinalysis with microscopy. These are all helpful. We look at all of this information in trying to determine is our patient developing lupus nephritis?

And I want to point out that it's very important that we quantify the protein in the urine, and that is why, specifically, I said a urine protein to creatinine ratio, it's not good enough just to do a urine dipstick. It's not sensitive or specific enough, and that is why we have to quantify the urine. And once the protein crosses a threshold, and you will see in the recent guidelines, EULAR and KDIGO, the threshold being 0.5 grams, once a patient reaches that threshold, we then take action in terms of getting the kidney biopsy to make the diagnosis.

But I do want to point out today for our listeners that there are plenty of data now that demonstrate that even lower levels of proteinuria, meaning 0.3, 0.4 grams, can be associated with aggressive forms of lupus nephritis, such as class 3 or class 4, as Dr. Kochar

mentioned. And thus, the field is moving towards earlier biopsy, because we know that the earlier that we can diagnose a patient and begin appropriate therapy, the better that patient will do, the more likely we can induce a renal response, and the better the long-term prognosis. And this will get to a concept that we will discuss later, which is the importance of early reduction in proteinuria to preserve long-term kidney health.

Now, once a patient is diagnosed with lupus nephritis, and we are following them in our clinic, we then have to make sure that we monitor them with a certain frequency to make sure that they are achieving a renal response. And if not, we have to adjust their medications. And so in terms of the frequency of monitoring, you will see in the updated EULAR recommendations and the KDIGO guidelines, a frequency of approximately every 3 months. However, when a patient has initially been diagnosed with lupus nephritis, and we are starting initial therapy, aggressive therapy up front, typically in the clinic, we monitor them with urinalysis, UPCR, serum creatinine on a monthly basis when they're in that very active stage of the treatment of lupus nephritis. And then we can decrease the frequency of monitoring to approximately every 3 months during that subsequent phase of treatment. Therefore, it's very important to remember early surveillance, active surveillance, make sure we diagnose lupus nephritis as early as possible. But then we have to monitor our patients carefully throughout the treatment course, to make sure that they sustain their renal response and to try to prevent the onset of lupus nephritis flares.

Dr. Turck:
And if we switch gears and talk a bit about treatment goals, Dr. Kochar, how do you achieve specific target goals? And how have the guideline updates impacted your approach?

Dr. Kochar:
So recently, the EULAR and KDIGO guidelines have been updated, and recommend aggressive goals for decreasing proteinuria and reducing steroid dose. The target proteinuria reductions that we are aiming for now are at least 25% by 3 months, 50% by 6 months, and a UPCR target below 0.5 to 0.7 mg/mg by 12 to 24 months, which is the definition of complete remission. And we are also aiming for target steroid reductions to 5 mg or less than 5 mg per day as early as possible to reduce the adverse effects that we see from longer courses of steroids and higher doses of steroids.

So based on these updates, my approach has also been more aggressive in how I take care of these patients. First and foremost, as Dr. Dall'Era also mentioned, I do consider individual patient-specific factors. And based on these new guidelines which recommend triple therapy as initial therapy, we now have options. The two FDA approved drugs that we have are belimumab, which is a B cell therapy, and we have voclosporin, which is a CNI. So now we are able to add one of these FDA approved drugs to our conventional therapy, and this helps with better outcomes, and this helps us to lower steroid doses from early on.

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and I'm speaking with doctors Maria Dall'Era and Tina Kochar about the recent guideline updates for managing lupus nephritis in adult patients with systemic lupus erythematosus.

So coming back to you, Dr. Dall'Era, let's turn our attention to the current treatment guidelines. Because, as I understand it, the EULAR guidelines recommend the use of combination therapy with CNIs or biologics for adult patients with active lupus nephritis. So can you provide insight on when you would choose a CNI?

Dr. Dall'Era:
Yes. As I mentioned earlier, the current updated EULAR recommendations and KDIGO guidelines support the use of triple immunosuppressive therapies for the initial treatment of lupus nephritis and then continuing into the subsequent phase of treatment. And one of those triple immunosuppressive regimens contains a calcineurin inhibitor, specifically voclosporin. Why is this important? And why is this helpful?

Calcineurin inhibitors, such as voclosporin, are very interesting molecules, and they are unique in their mechanisms of action. They reduce proteinuria by two distinct mechanisms. The first is the one that I think we are all familiar with, which is the reduction in immunologic activity of T cells. This is the immunologic effect of calcineurin inhibitors. But there is a second mechanism of action which is essential in the treatment of lupus nephritis, and that is the direct action on the actin cytoskeleton of the podocyte to stabilize that cytoskeleton, decrease podocyte apoptosis, preserve podocytes. And this is very important in that rapid reduction of proteinuria that we see when we use calcineurin inhibitors such as voclosporin.

When we think about voclosporin, there are important differences that distinguish voclosporin from the predecessor, conventional calcineurin inhibitors. Number one, voclosporin is more potent. It is approximately three to five times more potent. It binds more potently to cyclophilin, and that is one of the distinguishing factors. Also, there is less metabolic toxicity. We do not see changes in lipid levels. We don't see changes in blood glucose levels. We don't see any adverse profile in terms of electrolytes that we see, for example, with

the conventional calcineurin inhibitors. Also, importantly, with voclosporin, because of the predictable pharmacokinetic profile, we don't have to undergo therapeutic drug monitoring. And this is a big deal for our patients that are leading very busy lives. We don't have to monitor levels.

Dr. Turck:
With that being said, let's further explore voclosporin as a treatment option. Dr. Kochar, what did the AURORA 1 trial tell us about voclosporin's efficacy? And how does this align with the EULAR guideline updates?

Dr. Kochar:
Sure. So AURORA 1 is a multi-center, double-blind, randomized, phase 3 trial in which patients were given voclosporin, 23.7 mg twice a day, or three capsules twice a day, or placebo, in combination with mycophenolate mofetil 1 gram twice a day, and low-dose oral steroids. And I do want to emphasize the fact that they used low dose steroids. So this trial included a scheduled rapid taper from 20 to 25 mg per day at week 1, all the way down to 2.5 mg per day by week 16. And this was achieved in majority of the patients, more than 80% of the patients.

The primary endpoint of this trial was a complete renal response rate, and the criteria were similar to the updated guidelines with a UPCR less than or equal to 0.5 mg/mg. And in this trial, voclosporin did demonstrate superior efficacy versus placebo. And I also want to emphasize that, the partial remissions and complete remissions were achieved much faster. So patients achieved a complete renal response in a mean time of about 169 days, so less than 6 months versus almost a year without the addition of voclosporin in the control group. Same thing with partial response; the partial response was achieved in less than a month, a mean time of about 29 days, which was a secondary endpoint. This helps with long-term kidney survival. And based on this data and based on this trial I incorporate voclosporin early on. So I use triple therapy from the get go, and this approach also allows me to use lower dose of steroids. And I use the exact same protocol that we had for steroids in this trial.

Dr. Dall'Era:
We also know from the AURORA 1 trial and the variety of post-hoc analyses that were done, that voclosporin was more effective than placebo in a variety of different subgroups of patients, regardless of biopsies. We saw efficacy in class 3, class 4, and pure class 5, regardless of the baseline UPCR. We saw efficacy in patients with high levels of UPCR, low levels of UPCR, and we saw efficacy across self-reported races and ethnicities. So across the board, we saw that voclosporin was more effective than placebo in the AURORA 1 and the AURORA 2 clinical trials, which are the phase 3 trial and then the blinded extension.

So we feel very confident and optimistic about the use of triple immunosuppressive therapy, including the use of calcineurin inhibitors, such as voclosporin in our patients with lupus nephritis, using these therapies early to induce a renal response and then continue to use these therapies throughout the subsequent phase of treatment. And we now have data because of that 2-year blinded extension called AURORA 2, we now have 3 years of data for the use of voclosporin for the treatment of lupus nephritis. And importantly, we saw that the use of voclosporin was safe. We did not see any reductions in EGFR over the course of those 3 years, and we saw continued reduction in levels of proteinuria over that course of time, and a continued very good safety profile over that course of time.

Dr. Turck:
And if we continue zeroing in on the EULAR guidelines, Dr. Dall'Era, what did they tell us about treatment with combination therapy?

Dr. Dall'Era:
Yes. I think that the EULAR guidelines have been instrumental for us in giving us that understanding about the importance of using triple immunosuppressive therapy early in our initial treatment of patients with lupus nephritis, and then continuing therapy for at least 3 years after our patients achieve a renal response. And the background for this, again, just to remind everybody, is that our conventional therapies that we've been using for 50 years for the treatment of lupus nephritis are incompletely effective, only about 20 to 25% of our patients with conventional therapies will achieve a complete renal response by 6 months. And that's just not acceptable, because we know that the longer a patient has high levels of proteinuria, the worse their longer-term kidney outcome is going to be. We also know that our conventional therapies are associated with high rates of lupus nephritis flares. And we know that they're associated with significant rates of end-stage kidney disease, mortality, cardiovascular risk.

In addition to that, as Dr. Kochar mentioned, the calling out of doses of glucocorticoids, that we have to get those glucocorticoids down early, and that our goal is to get down to a dose of less than or equal to 5 mg a day of prednisone early. And we feel confident that we can achieve this because we now have this triple immunosuppressive therapy regimen that, in clinical trials, has demonstrated to us that we can use lower doses of glucocorticoids and get that dose down at a much earlier time point.

Dr. Turck:
Well, we've certainly covered a lot today, so before we close, I'd like to get some final takeaways from both of you on managing lupus

nephritis in adult patients with SLE, and particularly your thoughts on combination therapy with newer agents. Dr. Dall'Era, let's start with you.

Dr. Dall'Era:
The big picture here is we now have two sets of updated guidelines, both the EULAR recommendations, as well as KDIGO guidelines that support the use of triple immunosuppressive therapy along with lower doses of glucocorticoids right from the beginning of our treatment with lupus nephritis after diagnosis. And that is a critical update for all of us to understand. No longer do we have to start with our conventional agents, which are not completely effective, and wait for patients to worsen, we don't have to do that anymore. We can actually start early with triple immunosuppressive therapy, lower doses of glucocorticoids, get patients into a complete renal response, and then continue those same therapies while we taper glucocorticoids. And again, the recommendation is for at least 3 years after achievement of a renal response. This is absolutely essential, and it's a paradigm shift.

Dr. Turck:
Thanks, Dr. Dall'Era. And Dr. Kochar, I'll turn to you for the final word.

Dr. Kochar:
I just want to add a couple of things. I do focus on personalized treatment strategies considering patient-specific factors. I think that's really important. Majority of our patients are young patients, and we really need to spend the time with our patients and understand what would be the best treatment approach for each individual patient. And early diagnosis and treatment is really the key. Once we have made the diagnosis, I think we need to be aggressive in our approach and start with triple therapy from the get go so we are able to get these patients into remission faster and lower the dose of steroids.

Dr. Kochar:
And lastly, I believe a collaboration between rheumatologists and nephrologists is really important. I think we can diagnose these patients early on if we are on board together from the get go, and we can offer our patients the best treatment and ensure best long-term kidney survival for these patients.

Dr. Turck:
With those key takeaways in mind, I want to thank our guests, doctors Maria Dall'Era and Tina Kochar, for sharing their insights on the recent guideline updates for the management of lupus nephritis in adult patients with SLE. Dr. Dall'Era, Dr. Kochar, thank you both for joining us.

Dr. Kochar:
Thank you.

Dr. Dall'Era:
Thank you.

Announcer:
Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy. Monitor blood pressure regularly.

Neurotoxicity: LUPKYNIS, like other CNIs, may cause a spectrum of neurotoxicities: severe include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, and changes in mental status and/or motor and sensory functions. Monitor for neurologic symptoms.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs, including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia. Monitor serum potassium levels periodically.

QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner when dosed higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

Drug-Drug Interactions: Avoid co-administration of LUPKYNIS and strong CYP3A4 inhibitors or with strong or moderate CYP3A4

inducers. Co-administration of LUPKYNIS with strong CYP3A4 inhibitors is contraindicated. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors. Avoid use of LUPKYNIS with strong or moderate CYP3A4 inducers.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) were glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite.

SPECIFIC POPULATIONS

Pregnancy: Avoid use of LUPKYNIS.

Lactation: Consider the mother's clinical need of LUPKYNIS and any potential adverse effects to the breastfed infant when prescribing LUPKYNIS to a lactating woman.

Renal Impairment: LUPKYNIS is not recommended in patients with baseline eGFR ≤45 mL/min/1.73 m^2 unless benefit exceeds risk. If used in this population, reduce LUPKYNIS dose.

Hepatic Impairment: For mild or moderate hepatic impairment, reduce LUPKYNIS dose. Avoid use with severe hepatic impairment.

Please see full Prescribing Information including Boxed Warning and Medication Guide for additional Important Safety Information about LUPKYNIS at LUPKYNISpro.com.

This program was sponsored by Aurinia Pharmaceuticals. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!