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Triple Immunotherapy and Dual Steroid-Based Immunotherapy for Lupus Nephritis: A Comparative Analysis

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Triple vs Conventional Dual Immunosuppressive Therapy for Lupus Nephritis: A Comparative Analysis," is sponsored by Aurinia Pharmaceuticals.

Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD. I'm Dr. Charles Turck and I'm here with Dr. Maria Dall'Era. Today we'll be discussing results from a propensity analysis comparing the LUPKYNIS, voclosporin-based triple immunosuppressive therapy utilized in the AURA-LV/AURORA 1 studies with the dual regimen of conventional high-dose mycophenolate mofetil, MMF, intravenous cyclophosphamide, IVC, and high-dose glucocorticoid-based therapy used in the landmark ALMS trial.

Not only is Dr. Dall'Era Professor and Chief of Rheumatology at the University of California San Francisco, but she's also 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. It's a pleasure to be here today.

Dr. Turck:
Dr. Dall'Era is also the author on the abstract for the propensity analysis we will be discussing during this podcast.

Now, before we dive into our discussion, let's take a moment to review the indication, boxed warnings, and important safety information 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 explain the importance of diagnosing lupus nephritis early in the utility of having treatment targets?

Dr. Dall'Era:
It is very important to diagnose lupus nephritis early. And thus, when we suspect lupus nephritis in our patients with SLE, we want to obtain an early kidney biopsy, make that diagnosis, and start immunosuppressive therapy right away. And the reason for that is we want to prevent kidney damage as early as possible. We want to shut down that acute inflammation that's occurring so we can prevent the accrual of kidney damage.

One thing that we look at while we are treating our patients is proteinuria reduction. We can assess the reduction in proteinuria over time. Why is that important?

Well, we know that the earlier we can reduce proteinuria, the better the long-term kidney outcome for that particular patient. And I encourage all of you to listen to our Podcast 1 where we review in detail, the 2023 update of the EULAR recommendations for the management of lupus nephritis, and also the 2024 KDIGO guidelines for the management of lupus nephritis. And we describe the treatment targets in terms of proteinuria reduction.

Just to give you an overview again, we are aiming for at least a 25 percent reduction in proteinuria by 3 months after starting immunosuppressive therapy, a reduction of at least 50% in proteinuria by 6 months, and then we want to get down to between 0.5 and 0.7 grams per day of protein by month 12 after starting immunosuppressive therapy. So those are kind of landmarks that we can follow over the course of time as we follow our patients. And the idea here is that by using combinations of therapies that we're going to get to, we can actually hit those targets to a better degree.

Dr. Turck:
Before we jump into the propensity analysis, let's discuss the paradigm shift towards using triple immunosuppressive therapies. Dr. Dall'Era, what is meant by this term? And how does it differ from conventional dual therapy?

Dr. Dall'Era:
The way that I like to think about this is, we are using combinations of therapies that target different immunological and cellular pathways. Another way to think about it is we are targeting several vulnerabilities of lupus simultaneously, and this is the way that treatment is approached in the area of cancer therapy, for example. Targeting multiple pathways to be able to suppress inflammation and the immunological insult that is occurring in SLE.

In the context of this study that we will be discussing, triple immunosuppressive therapy refers to voclosporin plus a lower dose of mycophenolate mofetil at 2 grams a day, plus low-dose glucocorticoids. That is what we mean by triple immunosuppressive therapy.

This is distinct from the traditional way that we've been treating lupus nephritis for decades, which is with dual immunosuppressive therapy. And what that means is our conventional therapies, high-dose mycophenolate mofetil or cyclophosphamide plus high-dose glucocorticoids. So they're very different regimens, and we are now shifting towards the use of the triple immunosuppressive regimen up front to treat lupus nephritis.

Dr. Turck:
Thank you for that clarification, Dr. Dall'Era. And if we place these two treatment regimens in a clinical context and set the stage for our propensity analysis discussion, can you briefly describe the key trials that investigated them?

Dr. Dall'Era:
Yeah, so taking a step back, the overarching goal of the propensity analysis was to compare the safety and efficacy of the voclosporin-based triple immunosuppressive regimen that I described, compared to the conventional dual immunosuppressive regimen. So the question is, how do we do that? There's not a randomized controlled trial that compares those regimens head-to-head. So what is the

next best thing that we can do? Well, we can do a propensity analysis, and that is what we've done.

The trials that we drew from to be able to do this propensity analysis were the following. For the voclosporin group, we used the AURA-LV and the AURORA 1 trials. The AURA-LV was the phase 2 voclosporin trial, and the AURORA 1 was the phase 3 voclosporin trial. So we took patients from those trials for the voclosporin group. For the conventional group, we took patients from the ALMS trial. And if you all remember, the ALMS trial was a randomized controlled, open-label trial that compared high-dose mycophenolate mofetil with a target dose of 3 grams a day to monthly pulse IV cyclophosphamide. And all of the patients in the ALMS trial received high-dose glucocorticoids.

So the trials were very different, but the overarching theme here is in the voclosporin trials, it was the triple immunosuppressive regimen using voclosporin, a lower dose of mycophenolate mofetil, low-dose glucocorticoids. And the ALMS trial, it was high-dose conventional therapy plus high-dose glucocorticoids.

Dr. Turck:
So with that background in mind, let's jump into the propensity study. What were the goals, methodology, and endpoints?

Dr. Dall'Era:
The overarching goal was to compare the safety and efficacy of a voclosporin-based triple immunosuppressive regimen to a dual immunosuppressive regimen of conventional therapies, including high-dose glucocorticoids and high-dose mycophenolate mofetil. That's the overarching goal. And our hypothesis going into the study was that the voclosporin-based triple immunosuppressive therapy would have a better safety profile, but not compromise on efficacy.

And one might ask, why did we hypothesize that there would be an improved safety profile in the voclosporin group? And that is because the voclosporin group utilized lower-dose mycophenolate mofetil and lower-dose glucocorticoids. And for that reason, we hypothesized there would be better safety in the voclosporin group.

To do this study, we use propensity score methodology to generate two groups of matched participants, one group from the voclosporin trials that I mentioned, AURA-LV and AURORA 1, and the second group from the ALMS trial, and then we sub-stratified the ALMS patients by MMF or IV cyclophosphamide. We matched on key demographic and key clinical factors, so we had these nice, matched groups, and then we could compare the safety and the efficacy between the groups.

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Maria Dall'Era about the propensity analysis study comparing the Lupkynis-based triple immunosuppressive regimen versus the dual regimen of conventional high-dose MMF, IVC, and high-dose steroid immunosuppressive therapy.

So now that we know the goals and design of this propensity study, Dr. Dall'Era, what were the key outcomes of this analysis?

Dr. Dall'Era:
Let's start with the efficacy first. We found that the voclosporin-based triple immunosuppressive group had earlier and greater reductions in proteinuria compared to the conventional dual immunosuppressive group. And this is very important, because proteinuria is a key outcome measure in lupus nephritis and is predictive of long-term kidney health. The earlier we can reduce proteinuria, the better the long-term kidney outcomes for a particular patient.

We looked at proteinuria reduction at 3 months and 6 months. And we found at 3 months that a greater proportion of participants in the voclosporin group had at least a 25% reduction in proteinuria compared to the ALMS group. We found that at 6 months, a greater proportion of the voclosporin participants had a proteinuria reduction to less than or equal to 0.5 grams compared to the ALMS group. And we found at 6 months that a greater proportion of participants in the voclosporin group had at least a 50% reduction in proteinuria compared to the ALMS group. And as you recall from the beginning of this podcast, that 25% reduction in proteinuria at 3 months and 50% reduction in proteinuria at 6 months are key targets that we are trying to achieve. And those are targets that are outlined, for example, in the 2023 updated EULAR recommendations. These are targets that we can use in our clinical practice.

Another important outcome measure that we looked at in this study was the use of glucocorticoids. And not surprisingly, we found a lower cumulative dose of glucocorticoids in the voclosporin group compared to the ALMS group, and a lower mean daily dose of glucocorticoids in the voclosporin group compared to the ALMS group. And this is very important, because we know that glucocorticoids are a major factor in the accrual of organ damage in our patients with lupus, specifically damaged components such as avascular necrosis, osteoporosis, cardiovascular disease, cataracts, all of these.

That then leads me into talking more about safety. We found that the overall incidence of adverse events was higher in the ALMS group compared to the voclosporin group. And this was across multiple organ system domains, for example, gastrointestinal, mucocutaneous,

musculoskeletal, infections, infestations.

There were three specific adverse events in which we saw a higher frequency in the voclosporin group compared to ALMS, and those were eGFR decrease, hypertension, and anemia. I want to address the eGFR decrease and just remind all of our listeners that a decline in eGFR at the beginning of treatment is an expected effect of all calcineurin inhibitors. And we understand the mechanism very clearly, that there's vasoconstriction of the afferent arteriole leading into the glomerulus. What we see is a slight decline in eGFR at the beginning of therapy, and then stabilization over time. And if you all recall from the AURORA 1 trial, the decline in eGFR at the very beginning of initiation of therapy with the voclosporin-based regimens was between 2 to 3 mL/minute. And then there was stabilization of eGFR throughout the time course of AURORA 1 as well as through AURORA 2. And AURORA 2, if you remember, is the blinded, long-term extension of AURORA 1. So reassuringly, stabilization of eGFR across AURORA 1 and AURORA 2. Remember that hypertension is also an expected effect of calcineurin inhibitors.

Importantly, very few participants in the voclosporin trials had to stop therapy because of these adverse events; these were manageable and expected adverse events.

Dr. Turck:
Thanks for sharing those findings with us, Dr. Dall'Era.

Now, if we bring this into the real-world setting, what implication do these results have for patients? And what kinds of discussions do you have with them regarding voclosporin-based triple immunosuppressive therapy?

Dr. Dall'Era:
I'm so glad that you asked this question. I think this is absolutely key. How do we translate the findings from this study into clinical practice? How do we think about these findings in terms of how I take care of my patients in my day-to-day clinical practice of patients with lupus? This is the way that I am thinking about this paradigm shift. Just to remind everybody you know, for decades in the treatment of lupus nephritis we have been using dual immunosuppressive therapy with high-dose glucocorticoids, high-dose mycophenolate mofetil or cyclophosphamide, and now we are shifting to a new reality based on data from well-conducted trials, that we can be using these triple immunosuppressive regimens. But it's very important, I have found in my own practice, to spend time with my patients at the very beginning, explaining the rationale behind using these multiple therapies at once.

Because it can be quite overwhelming for a patient, particularly you can put yourself in the place of a patient. This is a new diagnosis of lupus perhaps, a new diagnosis of lupus nephritis, and we're asking them to take multiple medications at one time to treat this disease, and it can be overwhelming and scary for patients. And so I take a lot of time in the beginning and explain this is why I'm asking you to take all of these therapies up front. It's because I believe, and the data support, that by using combinations of therapies up front, we can better suppress the immunologic and inflammatory activity happening in your kidney right now, so we can preserve that kidney for the long term. And the thought is, we start out with multiple therapies at the beginning, get the lupus nephritis under control, get the proteinuria down, and then over the course of time, we can begin to peel back those medications.

It's a different paradigm than the old paradigm, which was start slow, start with one or two medications, and then build up if a patient doesn't respond. We don't think that's acceptable anymore, because with the old way of doing things, we know from biopsy studies that patients were continuing to accrue damage in their kidneys, and once that damage is there, it's not going away. And once that damage is there, that patient is closer to reaching end-stage kidney disease, and that's an unacceptable outcome, in my opinion. Therefore, it's worth trying to help our patients adhere to combinations of therapies early in the disease course, so we can shut down the immunologic process and improve their long-term kidney outcomes.

We also have to explain the fact that the triple immunosuppressive therapy regimen allows for lower doses of glucocorticoids. And we think about what is the number one medication that causes toxicity and damage in our patients is glucocorticoids. So we finally have a regimen in which we can reduce the dose of glucocorticoids.

And thus, the investment by using multiple therapies at once is we can suppress disease activity and we can use lower doses of glucocorticoids, and both of those factors will result in a decrease in organ damage, and particularly preservation of the kidney. And that's really what we're aiming for.

Dr. Turck:
Well, we've certainly covered a lot today. But before we close, I'd like to get some final key takeaways from you, Dr. Dall'Era.

Dr. Dall'Era:
Yes. Number one, it's important to diagnose lupus nephritis as early as possible and start immunosuppressive therapy as early as possible so we can reduce proteinuria and we can improve long-term kidney outcomes.

Secondly, the way that we do that is by using triple immunosuppressive therapy, combination therapy, such that we can improve the safety of the older regimens, and we can improve outcomes. And the way that we did this in this study was by using a voclosporin immunosuppressive-based triple therapy.

Dr. Turck:
Well, with these key takeaways in mind, I want to thank our guest, Dr. Maria Dall'Era, for sharing her insights on the assessment of a voclosporin-based triple immunosuppressive therapy for lupus nephritis. Dr. Dall'Era, it was great speaking with you today.

Dr. Dall'Era:
It was great speaking with you as well. Thank you for inviting me to participate today in this discussion.

Dr. Turck:
For ReachMD, I'm Dr. Charles Turck. Please stay tuned for some additional important safety information.

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.

Announcer:
This program was sponsored by Aurinia Pharmaceuticals. If you missed any part of this discussion, visit Industry Features on

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