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**JOURNAL CLUB**

# Journal Club: Efficacy and Safety of Voclosporin Versus Placebo for Lupus Nephritis (AURORA 1): A Double-Blind, Randomized, Multicenter, Placebo-Controlled, Phase 3 Trial

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**Objective.** Voclosporin, a novel calcineurin inhibitor approved for the treatment of adults with lupus nephritis (LN), improved complete renal response rates in patients with LN in a phase 2 trial. This study aimed to evaluate the efficacy and safety of voclosporin for the treatment of LN.

**Methods.** This multicenter, double-blind, randomized phase 3 trial was done in 142 hospitals and clinics across 27 countries. Patients with a diagnosis of systemic lupus erythematosus and LN, according to the American College of Rheumatology criteria, who had undergone a kidney biopsy within 2 years that showed class III, IV, or V (alone or in combination with class III or IV) were eligible for this study. Patients were randomly assigned (1:1) to receive oral voclosporin (23.7 mg twice daily) or a placebo, on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids, by use of an interactive web response system. The primary endpoint was complete renal response at 52 weeks, defined as a composite of urine protein creatinine ratio of 0.5 mg/mg or less, stable renal function (defined as estimated glomerular filtration rate [eGFR] ≥60 ml/min/1.73m$^2$ or no confirmed decrease from baseline in eGFR of > 20%), no administration of rescue medication, and no more than 10 mg prednisone equivalent per day for 3 or more consecutive days or 7 or more days during Week 44 through Week 52 (just before the primary endpoint assessment). Safety was also assessed. Efficacy analysis was by intention to treat, and safety analysis was by randomized patients receiving at least one dose of study treatment.

**Results.** Between April 13, 2017, and October 10, 2019, 179 patients were assigned to the voclosporin group and 178 were assigned to the placebo group. The primary endpoint of complete renal response at Week 52 was achieved in significantly more patients in the voclosporin group than in the placebo group (73 [41%] of 179 patients vs 40 [23%] of 178 patients; odds ratio, 2.65; 95% confidence interval [CI] 1.64-4.27; $P < 0{\cdot}0001$). The adverse event profile was balanced between the two groups; serious adverse events occurred in 37 (21%) of 178 patients in the voclosporin group and 38 (21%) of 178 patients in the placebo group. The most frequent serious adverse event involving infection was pneumonia, occurring in seven (4%) patients in the voclosporin group and in eight (4%) patients in the placebo group. A total of six patients died during the study or study follow-up period (one [<1%] patient in the voclosporin group and five [3%] patients in the placebo group). None of the events leading to death were considered by the investigators to be related to the study treatments.

**Conclusion.** Voclosporin in combination with mycophenolate mofetil (MMF) and low-dose steroids led to a clinically and statistically superior complete renal response rate versus MMF and low-dose steroids alone, with a comparable safety profile. This finding is an important advancement in the treatment of patients with active LN.

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## INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with a wide spectrum of clinical phenotypes (1). From these, lupus nephritis (LN) is arguably the most common serious manifestation that can present with proteinuria, hematuria, and/or creatinine elevation (2). The severity of renal disease in lupus, which, if left untreated, leads to kidney failure, is influenced by different demographics and clinico-pathological factors (3–4). Current therapeutic interventions with systemic glucocorticoids and cyclophosphamide or mycophenolate have resulted in improved renal responses in patients with LN; however, a significant proportion of patients with LN still relapse or progress to end-stage kidney disease (5). Although end-stage renal disease is regarded as the standard endpoint in LN trials, a significant body of evidence has established the role of proteinuria as an important biomarker for long-term kidney outcomes (6).

Over the last decade, mycophenolate mofetil in combination with corticosteroids has gradually come to be regarded as the standard of care (SoC) in LN. Studies, primarily in Asia, suggested that combination therapy of mycophenolate, corticosteroids, and calcineurin inhibitors (CNIs) has shown greater renal responses than the SoC (7). Based on the unmet need in LN treatment, voclosporin, a new CNI agent, was evaluated in LN. The pharmacokinetic properties of voclosporin make frequent therapeutic monitoring unnecessary, and interactions with mycophenolic acid are less likely than the traditional CNIs cyclosporin and tacrolimus. A phase 2 trial-Aurinia Urinary Protein Reduction Active-Lupus With Voclosporin (AURA-LV), demonstrated that voclosporin in conjunction with the SoC was superior to the SoC alone in achieving complete renal responses (CRRs) at 24 weeks (8). These results led to the design of the Aurinia Renal Response in Active Lupus With Voclosporin (AURORA) that further analyzed the efficacy and safety of voclosporin as an add-on therapy in LN when compared with placebo (9).

## PATIENTS AND METHODS

**Trial design.** This was a phase 3, randomized, placebo-controlled, double-blind, international multicenter trial conducted in 142 clinical sites across 27 countries. Aurinia Pharmaceuticals sponsored and conducted the study in its totality.

**Eligibility criteria.** At enrollment, adults were eligible if they met the revised American College of Rheumatology classification criteria (1997) for SLE and had confirmed biopsy-proven class III, IV, or V (alone or in combination with class III or IV) nephritis with active renal disease predefined as a urine protein creatinine ratio (UPCR) at screening of 1.5 mg/mg or more (class III or IV) or 2 mg/mg or more (pure class V) if the kidney biopsy result was within 6 months. Participants who had a kidney biopsy result more than 6 months (up to 2 years) prior to screening required a twofold increase in the UPCR within 6 months of enrollment. Excluded patients were those whose estimated glomerular filtration rate (eGFR) at screening was 45 ml/min/1.73 $m^2$ or less.

**Trial procedures.** Eligible patients were equally allocated to receive oral voclosporin at a dose of 23.7 mg (intervention arm) or "identical" matching placebo (control arm) twice daily for a 52-week period. These patients were further stratified at randomization by considering different prognostic factors (biopsy class, use of mycophenolate mofetil [MMF], and region). To account for the potential hemodynamic effects (renal vasoconstriction) observed with CNIs, the study included guidance to stop or decrease the voclosporin dose depending on the reduction of eGFR. Furthermore, withholding the study drug was recommended in patients with a systolic blood pressure of 165 mm Hg or more or diastolic blood pressure of 105 mm Hg or more plus symptomatic hypertension. The experimental and control groups received weight-based dosing of intravenous methylprednisolone daily (<45 kg = 0.25 g/day methylprednisolone; ≥45 kg = 0.5 g/day methylprednisolone) during Days 1 and 2. Thereafter, per the predefined protocol, patients in both arms were transitioned to a weight-based oral prednisone taper starting at Week 2, with a subsequent drop to 5 mg/day at Week 8 and 2.5 mg/day at Week 16. Dose adjustments were allowed at investigator discretion after the prednisone taper schedule was completed. MMF (up to 2 g daily) was permitted as background therapy in all patients at screening or during the initiation of the study. Further up-titration needed the approval of the medical monitor. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for hypertension was allowed as long as the dose was stable 4 weeks before randomization and without dose changes during the trial. Close monitoring of UPCR was performed every 1 to 6 weeks, including two 24-hour urine collections at Week 24 and 52. Additional clinico-serologic disease activity and safety parameters were assessed at baseline, Week 24, and Week 52.

**Efficacy and safety endpoints and statistical analysis.** The primary outcome was a CRR, set as a composite of UPCR of 0.5 mg/mg or less, eGFR of 60 ml/min or more or no change of 20% or more from baseline, no receipt of rescue medication for LN, and no use of 10 mg prednisone for 3 days or more or for 7 days or more in total during Week 44 through Week 52. To limit the inflation of type 1 error risk by testing multiple endpoints, a hierarchical test procedure (Hochberg sequential model) was used to rank key secondary outcomes that resulted as follows: 1) time to UPCR of 0.5 mg/mg or less; 2) partial renal response defined as 50% or more reduction from the baseline UPCR at Weeks 24 and 52; 3) time to 50% reduction in UPCR from baseline; and 4) CRR at Week 24. It is worth mentioning that additional endpoints were assessed, but these did not end up being ranked by the hierarchical model. The minimum number of subjects

needed was estimated to be 162 in each group, corresponding with 80% power to detect a significant difference in CRR (14.4%; odds ratio [OR], 2.1) between the study drug and the placebo. Efficacy endpoints (primary and hierarchical secondary endpoints) were analyzed in the intention-to-treat population. Although not sufficiently powered, subgroup analyses evaluating the primary endpoint were done using prespecified variables: age (≤30 years vs >30 years), sex (male vs female); race (white vs Asian vs other), region (Asian-Pacific vs Europe and South Africa vs Latin America vs North America), class (class V vs other), use of MMF at screening (yes versus no), and MMF dose (≤2 g/day vs >2 g/day). Patients who withdrew from the study were assigned as nonresponders. Time-to-event data were analyzed with Kaplan-Meier curves. A full list of the analyses was appropriately specified and shown in the original paper.

## RESULTS

A total of 357 subjects were ultimately recruited between April 2017 and October 2019; from these, 179 patients were assigned to the voclosporin arm and 178 patients were assigned to the placebo arm, representing the intention-to-treat population. One patient in the intervention arm did not start the study drug because of an adverse event. At the end of the trial, 163 subjects completed the protocol in the voclosporin group and 147 completed the protocol in the placebo group. The majority of the patients in both groups who terminated the study early withdrew their consent.

Baseline characteristics were similar in both groups and, as expected, a higher percentage of patients were women, with a median age of 31 to 32 years. Most subjects in the study were non-Hispanic white or Asian. The mean times from initial SLE and LN diagnoses to study enrollment were 4.6 to 4.7 years and 6.6 to 6.9 years, respectively. Histological class IV LN accounted for half of the biopsy results. Of all the biopsies, 89% were obtained within 6 months before screening. The subjects' mean baseline eGFR was 90.4 to 92.1 ml/min/1.73 $m^2$, with approximately 80% having an eGFR of 60 ml or more/min/1.73 $m^2$. Additionally, the mean baseline UPCR ranged from 3.87 mg/mg to 4.14 mg/mg. Lupus disease activity markers such as low complement levels and high anti–double-stranded-DNA titers were frequently abnormal, in line with a mild to moderate activity index assessed by the SELENA-SLEDAI score. Nearly 50% of patients were using MMF at screening, and the mean daily dose used throughout the study was 2 g daily in both groups. Only four individuals in the intervention group and six in the control group were taking 3 g/day MMF during the whole study. Eighty-one percent of patients in the control group and 82% of patients in the voclosporin group were able to taper prednisone to 2.5 mg daily or less at Week 16 in line with the guidance; though by Week 52, the percentage of patients on these reduced doses of prednisone declined to 73% and 75%, respectively.

The results with respect to the primary endpoint showed a significantly higher proportion of patients in the voclosporin group (41%) achieving a CRR when compared with the placebo group (23%). Even though all endpoints of the CRR were numerically higher in the voclosporin group than in the placebo group, the statistically meaningful effect was mainly driven by the UPCR component. In addition to CRR at 52 weeks, ranked secondary endpoints, including CRR at 24 weeks and partial renal response at 24 and 52 weeks, demonstrated significant differences between the groups (favoring the voclosporin group). Moreover, time-to-event plots indicated that patients in the intervention arm reached a UPCR of 0.5 mg/mg or less or a 50% reduction in UPCR significantly faster than those in the placebo arm. Roughly starting at Week 2, more patients receiving voclosporin achieved UPCR targets than those receiving placebo, and these differences were sustained through Week 52. Analysis of change from baseline in immunology parameters and SELENA-SLEDAI index scores did not show any significant differences between the groups. Lastly, all subgroup analysis indicated a greater CRR in the intervention arm than in the placebo arm, and these results were significant for the following: both sex and ages, Asian-Pacific and Latin America region, other than pure class V, use of MMF at screening, and a maximum MMF dose of 2 g/day or less. Additionally, post hoc analyses of race and ethnicities were significant for Asian, Black, and for both ethnic groups.

Safety analysis results displayed comparable adverse events between both groups. From these, serious adverse events were seen in 37 patients in the voclosporin arm and in 38 patients in the placebo arm. Half of these cases were due to infections, with the most common being pneumonia. An identical number of treatment-related serious adverse events were recorded, with eight in each group. A total of five patients died in the placebo group, and one died in the intervention group. The cause of death of the patient receiving voclosporin was related to nosocomial pneumonia. The rest of the causes of death in the placebo arm were pneumonia, septic shock, LN, pulmonary embolism, and acute respiratory failure. Three events (two in the placebo group and one in the voclosporin group) happened 30 days after stopping the study drug. The investigators reported that none of the deaths were directly attributed to the treatment. The metabolic profile in terms of hemoglobin A1C and glucose levels was unchanged from baseline in both groups. No new-onset diabetes was reported in the voclosporin group. Noticeable, though, was a significantly greater drop from baseline in the mean cholesterol and low-density lipoprotein cholesterol levels at Week 52 in the voclosporin group when compared with the placebo group. Both groups had normal mean values of serum electrolytes throughout the study. A minimal transient decrease in the eGFR was observed in the voclosporin group between Weeks 2 and 4, but the least square means analysis of corrected eGFR from Weeks 4 to 52 showed a positive slope for voclosporin. Drug discontinuation based on eGFR reduction was 2% in both groups, and,

per the investigator, serious renal dysfunction was seen in 3% in the voclosporin group. Finally, at Week 2, the mean systolic blood pressure increased 3.9 mm Hg in the voclosporin group, with a later drop to baseline by Week 8.

## DISCUSSION

LN can be a devastating disease, causing high morbidity and mortality in patients with SLE. Existing off-label immunosuppressive management in the last two decades has decreased poor outcomes in LN. Furthermore, the newly U.S. Food and Drug Administration (FDA)–approved drug belimumab promises improved renal responses (10). Despite these advances in LN, up to 60% of patients do not achieve CRR; of these, half of the patients may experience subsequent flares, and one-third may develop end stage renal disease (ESRD). Based on the ongoing need for new therapeutic approaches, the AURORA 1 phase 3 trial investigated the efficacy and safety of voclosporin, a new generation CNI, plus SoC versus SoC alone in patients with LN. In brief, the primary endpoint (CRR at Week 52) was met by 41% of patients in the voclosporin group and 23% of patients in the placebo group, resulting in an absolute risk reduction of 18% and an OR of 2.65 (CI, 1.64-4.27; $P < 0.0001$) in favor of voclosporin. Hierarchical secondary endpoints showed similarly favorable results. In regard to the safety profile, the rate of adverse events in the voclosporin plus MMF and steroids group was comparable with that in the control group. More importantly, voclosporin was not associated with increased mortality, as was seen in the phase 2 trial.

These results confirmed the enhanced effect voclosporin has when added to a background of MMF and steroids in patients with biopsy-proven active LN. If these results are expressed as a number needed to treat, on average, five patients would need to be treated with voclosporin plus SoC for 52 weeks (instead of SoC alone) for one additional patient to achieve a CRR. Importantly, the study included patients with active proliferative glomerulonephritis who most likely benefit from escalating immunosuppression. It is essential also to highlight that patient dropout was minimal; most patients had good drug adherence despite a substantial pill burden, and few patients discontinued the drug because of serious adverse events. One last point is that, although the primary outcome was CRR and not renal replacement therapy or death, CRR and especially its most important component, UPCR, is a surrogate endpoint recognized as the best predictor of long-term kidney preservation in LN.

A limitation of the study was the exclusion of patients with a moderate to severe reduction of eGFR. Therefore, the efficacy and especially the safety of voclosporin in these severe LN cases remains unknown. Additionally, histopathological activity and chronicity indexes were not evaluated, making it hard to assess the effect of voclosporin on inflammation versus specifically on proteinuria. Despite recruiting participants who were already receiving MMF, the study could not reach any conclusions regarding treatment responses between new-onset LN and relapse/resistant LN because of the fact that data about MMF dose and pre-enrollment treatment duration were not collected. Also important to note is that this trial, similarly to most studies in LN, did not include patients receiving cyclophosphamide as an induction strategy. Regarding the primary outcome, it is worth mentioning that, of the four critical endpoints of the composite CRR, only one achieved statistical significance (UPCR $\leq$ 0.5 mg/mg). In other words, although voclosporin may significantly reduce proteinuria in LN, there is no clinically meaningful difference in the use of rescue medication, prednisone use, or eGFR mean values between both groups. Patient-related outcomes were not included.

The novel prednisone regimen employed in the trial is an interesting alternative that could potentially minimize risks and be effective in LN, as claimed by the authors after comparing rates of renal responses with historical controls using steroids at a high dose with a prolonged taper. However, these claims need to be explored in future trials with a concurrent control group. Although voclosporin demonstrated a reduction of protein in the urine, there was no apparent effect on immunological parameters. This raises the question of whether voclosporin benefited the patients through its antiproteinuric effect and not its immunosuppressive effect. Lastly, the duration of the study (52 weeks) cannot address long-term outcomes such as subsequent flare prevention, progression to ESRD, or long-term safety. That being said, an ongoing extension of this study (NCT03597464) will be able to answer these important questions.

In conclusion, the addition of voclosporin to MMF and low-dose steroids was efficacious in LN with an acceptable safety profile. On the basis of these data, the FDA approved the first oral therapy for LN in January 2021, bringing encouraging news into this field. Now, we are eagerly awaiting to see the impact voclosporin will have in real practice and suspect that the economic burden would play a major role in its applicability.

## AUTHOR CONTRIBUTIONS

Drs. Rubio and Kyttaris drafted the article, revised it critically for important intellectual content, approved the final version to be published, and take responsibility for the integrity of the data and the accuracy of the data analysis.

## ROLE OF THE STUDY SPONSOR

Aurinia Pharmaceuticals was involved in data collection, data analysis, interpretation of data, medical writing support and reviewed the final manuscript before submission. Editorial control was retained by the authors. Publication of this article was not contingent upon approval by Aurinia Pharmaceuticals.

## REFERENCES

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011;365:2110–21.

2. Anders H-J, Saxena R, Zhao M-H, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primers 2020;6:7.
3. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford) 2016;55:252–62.
4. Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. Arthritis Rheumatol 2015;67:1305–13.
5. Tektonidou MG, Dasgupta A, Ward MM. Risk of end-stage renal disease in patients with lupus nephritis, 1971–2015: a systematic review and bayesian meta-analysis. Arthritis Rheumatol 2016;68:1432–41.
6. Tamirou F, Lauwerys BR, Dall'Era M, Mackay M, Rovin B, Cervera R, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. Lupus Sci Med 2015;2:e000123.
7. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med 2015;162:18–26.
8. Rovin BH, Solomons N, Pendergraft WF, Dooley MA, Tumlin J, Romero-Diaz J, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. Kidney Int 2019;95:219–31.
9. Rovin BH, Teng YK, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2021;397:2070–80.
10. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YK, Contreras G, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med 2020;383:1117–28.