



Expanding therapeutic horizons of calcineurin inhibitors in lupus nephritis: from tacrolimus to next-generation agents

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Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus and remains a key determinant of long-term renal and overall outcomes. Over the past two decades, immunosuppressive therapy for LN has evolved substantially, with tacrolimus and other calcineurin inhibitors (CNIs) emerging as key treatment components. CNIs exert dual actions by suppressing T cell activation through calcineurin inhibition and stabilizing podocytes to reduce proteinuria [1,2]. Early clinical experience with cyclosporine demonstrated these effects; however, its use was limited by nephrotoxicity and metabolic complications [3]. Tacrolimus is a more potent and metabolically favorable alternative, and its use has expanded, especially in Asian countries [4,5].

Kim et al. [6] conducted one of the largest real-world analyses of long-term tacrolimus maintenance therapy for LN. Among 179 patients with biopsy-proven disease, 92 received tacrolimus, mostly in combination with mycophenolate mofetil. Over a five-year follow-up, the renal response rate exceeded 70%, and renal flare-free survival was similar to that observed in patients treated without CNIs. Importantly, no increase in serious infections, cardiovascular events, malignancies, or decline in kidney function was observed in the tacrolimus group. These findings reaffirm that tacrolimus can be safely used over a long period in appropriately selected patients.

Earlier randomized trials from East Asia have demonstrated the efficacy of tacrolimus in both the induction and

maintenance phases of LN, particularly for membranous or mixed proliferative diseases [4,5,7]. These studies typically reported rapid reductions in proteinuria, with complete response rates approaching 60–70 percent at one to two years. However, most early evidence was derived from relatively short follow-up periods and selected patient groups. In contrast, the current study provides five-year outcomes in an unselected real-world cohort, strengthening the external validity of these earlier observations. The fact that long-term renal outcomes were comparable to those achieved with conventional regimens despite a higher baseline disease burden in the tacrolimus group is clinically meaningful.

The role of CNIs in LN has further evolved with the introduction of voclosporin, which has more stable pharmacokinetics and reduces the need for therapeutic drug monitoring. In the AURORA 1 trial, voclosporin combined with mycophenolate and low-dose steroids achieved significantly higher renal response rates than the placebo [8]. These results have expanded the options available to clinicians, especially for patients requiring rapid proteinuria reduction or steroid minimization. Although cyclosporine has become less common due to its metabolic profile, it still plays a role in selected cases, particularly when short-term proteinuria control is needed [3].

Multitarget therapy, which combines tacrolimus and mycophenolate with reduced steroid exposure, has gained increasing acceptance. Controlled studies have shown superior efficacy compared to cyclophosphamide-based regimens, especially for inducing remission in Class III, IV, and V diseases [9,10]. In this study, nearly 80 percent of the tacrolim-

us-treated patients received combination therapy, reflecting this trend. Notably, despite more severe disease at baseline, the long-term outcomes remained similar, supporting the effectiveness of multitarget strategies in real-world settings.

Similar to the CNI therapy, safety remains a key consideration. However, cyclosporine is associated with nephrotoxicity, hypertension, and metabolic complications. Tacrolimus has a favorable safety profile, and Kim et al. [6] observed stable kidney function over five years. Voclosporin may offer additional advantages through predictable exposure and potentially lower nephrotoxicity, although long-term data are required [8]. These findings highlight the importance of individualized dosing, careful monitoring, and patient selection to maximize therapeutic benefits. In Korea, voclosporin is not yet available in clinical practice, making real-world evidence supporting the use of tacrolimus particularly valuable. Unlike voclosporin, tacrolimus has been widely used for many years, and accumulating clinical data in Asian populations provide important insights into its efficacy and safety.

This body of evidence allows clinicians to make informed treatment decisions and offers a practical therapeutic option for patients with LN who may otherwise have limited access to newer agents. This study has several limitations that require careful attention. It was retrospective in nature and conducted at a single center with inherent selection bias. The tacrolimus group had more severe disease at baseline, which may have influenced the early response rate. Tacrolimus exposure and blood level monitoring were not standardized, and no histological evaluation was performed to assess tissue-level remission. These factors limit the mechanistic interpretation and preclude definitive conclusions regarding optimal dosing or treatment duration.

Nonetheless, the clinical implications of these findings remain significant. These findings support tacrolimus as an effective and safe maintenance option for LN, particularly in patients with refractory or membranous diseases. They also provided real-world evidence that complemented the results of previous controlled studies. In clinical practice, the choice between tacrolimus and voclosporin depends on disease characteristics, comorbidities, drug availability, and cost. The possibility of reducing steroid exposure through CNI-based multi-target therapy represents an additional benefit.

Future research should address several important issues. First, prospective multicenter comparative trials are needed to clarify the relative benefits and risks of tacrolimus, voclo-

sporin, and cyclosporine in different LN subtypes. Second, standardized therapeutic drug-monitoring strategies should be developed to balance efficacy and safety. Third, mechanistic studies integrating biomarkers, repeat renal biopsy, or noninvasive molecular signatures could help identify patients most likely to benefit from specific CNIs. Finally, long-term data on renal survival, cardiovascular outcomes, and patient-reported outcomes are essential to fully define the role of CNIs in LN management.

In summary, the findings of Kim et al. [6] provided robust real-world evidence supporting tacrolimus as a valuable maintenance therapy for LN. They built on earlier randomized trials and extended the evidence base to a broader patient population with a long-term follow-up. Together with emerging data on voclosporin and the established experience with cyclosporine, these results indicate a new stage in LN therapy, where CNIs can be integrated into individualized combination-based strategies aimed at maximizing renal preservation and minimizing treatment-related toxicity.

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