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# Increasing Options for First-Line Therapy in Primary FSGS?

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Focal segmental glomerulosclerosis (FSGS) is a common pathologic diagnosis on kidney biopsy. It denotes focal and segmental intracapillary hyaline deposition and/or focal adhesions of capillaries to Bowman's capsule.[1,2] When it occurs without underlying alternate modes of kidney disease, together with the nephrotic syndrome and diffuse effacement of podocyte foot processes, it is likely to be deemed primary or idiopathic. This suggests that there is a circulating podocyte toxin, of unknown etiology, and that there is a poor prognosis when the disease goes untreated, with up to an 80% chance of kidney failure over 10 years.[3] However, it also suggests the possibility of response to immunosuppressive drugs, especially early in the disease course.

Over the past half century, the popularity of immunosuppressive therapy has waxed and waned, but overall review of data suggest that approximately one-half of patients with FSGS can respond to prolonged, high-dose oral steroids with a partial, or more rarely, complete remission.[4] This is defined by a substantial reduction in proteinuria, which has been linked with much improved outcomes in terms of kidney function and freedom from dialysis. Many patients (up to half of the responders to steroids) relapse and eventually become dependent on moderate doses of steroids or later become resistant. This has led to the use of other immunosuppressive strategies, such as using cyclophosphamide, mycophenolates, or calcineurin inhibitors to maintain proteinuria remission. Calcineurin inhibitors (CNIs) have been proven effective, even in cases in which patients were initially steroid resistant, and are broadly considered second-line therapy for individuals with FSGS.[4,5] In fact, the Kidney Disease International Guideline Organization suggests exactly that, patients with primary FSGS should receive prolonged steroids as first-line therapy, and those patients intolerant or inadequately responsive to corticosteroids should consider CNIs.[6]

However, the toxicity of prolonged doses of steroids are well known. Ranging from mood disorders, bone disease, and life-threatening infection, a prolonged course of steroids for FSGS is perilous. It is also frequently ineffective, requiring rescue therapy with CNIs. CNIs are well tolerated in general, with limited risks of infection, but renal dysfunction is a concern and the drug is variably absorbed and metabolized, such that serial drug levels and serum creatinine need to be closely monitored (trials have generally excluded patients with estimated glomerular filtration rate $<40$ ml/min). Still, many caregivers for patients with primary FSGS wonder whether it is not more reasonable to start with CNI therapy, rather than endure the adverse side effects and uncertainties of corticosteroids. Many, according to discussions in the corridors, and preliminary data from consortiums already do. Of course, it would be quite useful to know how the treatments, corticosteroids, or CNIs truly compare. To date, we have only small, uncontrolled studies or retrospective and small analyses that do support the comparative efficacy and tolerability of first-line CNI therapy as compared with steroids.[7–9]

In this issue of *KI Reports*, Chávez-Mendoza and colleagues[10] present a retrospective cohort analysis in patients with primary FSGS diagnosed between 2007 and 2014. This allows them to comment on 11 patients who were treated with first-line CNI therapy, which they compare to patients treated first-line with steroids, or others who failed steroids and were then rescued with CNI therapy. The patients were carefully selected, meeting criteria for the nephrotic syndrome, with heavy proteinuria, hypoalbuminemia, and hyperlipidemia. Only a minority had electron microscopy available, but among those who did, all had more than 80% foot process effacement. Almost all were treated with renin angiotensin system inhibitors (RAASi). Keep in mind that all patients in this analysis received

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some steroids. The steroid-treated group received 0.8 to 1.0 mg/kg daily for at least 12 weeks, and those receiving CNIs also received 0.1 to 0.15 mg/kg daily for an undefined period of time. The main study result is that there was no statistical difference in outcome between the primary treatment with steroid alone or with combined CNI and low-dose steroid. Similar, unusually good, rates of complete and partial remission were seen with either approach (77% response with 49% complete remissions in the steroid-alone group and 73% response with 36% complete remission in the CNI-steroid group). The very high response rate may in part be due to the population's slightly young age, relative freedom from perihilar FSGS, excluding collapsing lesions and relatively intact glomerular filtration rate at baseline, but are still higher than most reports in the literature. Regardless, the steroid-first arm and CNI-steroid–first arms were similar in response rates and time to response, similar in freedom from progression (doubling of creatinine or end-stage renal disease) and similar in relapses, which, as is typical, did ultimately occur in nearly 50% of responders in all groups. As best can be assessed, tacrolimus and cyclosporine performed similarly. The steroid-resistant group responded to rescue CNI-steroids, but required the highest exposure to steroids. Importantly, adverse events were assessed among this cohort. With its small size, statistical differences were limited, but there was a trend toward more infection, more classic steroid adverse events (psychiatric, dyspeptic), but fewer episodes of acute kidney injury in the steroid-first group compared with the CNI-steroid groups.

This small, retrospective experience adds to the other, admittedly small, studies to suggest that CNIs are indeed equally effective and at least as safe as steroids as primary therapy in FSGS (see Supplementary References). Although each of these studies is flawed by small numbers, incompletely described subjects, and limited follow-up and description of treatment of relapses, they give consistent results. This, at the very least, supports the fact that CNI therapy is a viable alternative to steroid therapy in patients intolerant or at the highest risk of steroid complications. It may also tip the scales, and provide enough cumulative evidence that first-line CNI therapy is safe and effective enough to replace steroids in any patient with primary FSGS, particularly when kidney function is relatively preserved (see Figure 1). It has long been our goal to avoid chronic treatment with steroids in the hope of avoiding their many side effects, both short-term and long-term. However, clear differences in adverse events have not been demonstrated in trials, cost differences of the at least 10 times more expensive CNI approach need to be accounted for, and legitimate concerns for the intrinsic nephrotoxicity of CNIs do, in some part, limit the enthusiasm for wholesale endorsement of a CNI-first approach.

Larger analyses of patients with primary FSGS should be forthcoming from cohorts such as NEPTUNE and CURE GN.[S2] Other insights might come from a clinical trial of another CNI, voclosporin, presently being tested as first-line treatment in patients with FSGS.[S3] Hopefully, these can more clearly determine if CNI-alone therapy, without steroids, is an equally effective and better tolerated treatment than long-term steroids, perhaps considering cost-effectiveness and how to best limit the small risks of nephrotoxicity. Until then, I will generally advise my patients as best possible

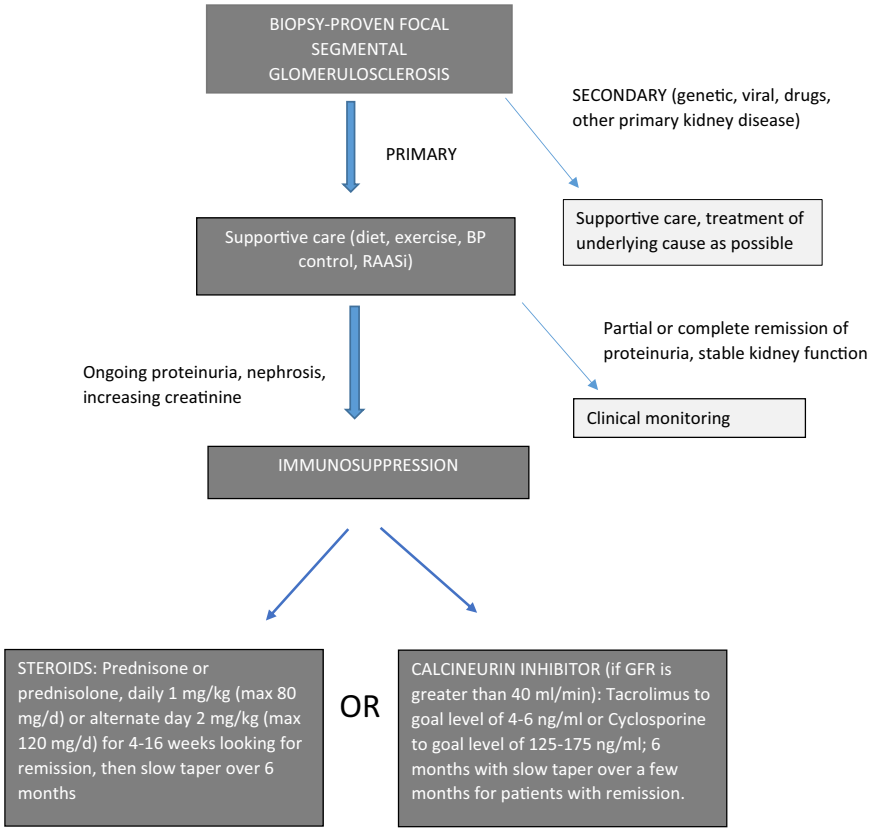


**Figure 1.** First-line care in patients with focal segmental glomerulosclerosis, a potential approach. BP, blood pressure; GFR, glomerular filtration rate; RASSi, renin angiotensin system inhibitor.

on their treatment options and continue my personal bias toward starting with CNI monotherapy or enrolling them in trials.

Finally, these approaches are already somewhat dated with initial trials of CNI in FSGS since the mid-1990s and steroids for the past 50 years. Neither of these approaches are as effective, durable, or safe as we would like. Further studies into the mechanism of the disease, the identification of the podocyte toxic factor, and trials of more novel approaches to therapy are desperately needed and anticipated.

## DISCLOSURE

RAL is a consultant for Rigel, Mallinckrodt, Fibrogen, Calliditas, and Omeros and receives study support from Rigel, Mallinckrodt, Fibrogen, Calliditas, Omeros, Retrophin, Cara, and Chemocentryx.

## SUPPLEMENTARY MATERIAL

**Supplementary References.**

Supplementary material is linked to the online version of the paper at http://www.kireports.org/.

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