Impact of the National Institutes of Health Focal Segmental Glomerulosclerosis (NIH FSGS) clinical trial on the treatment of steroid-resistant FSGS

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ABSTRACT

Idiopathic focal segmental glomerulosclerosis (FSGS) is among the most common, morbid and treatment-resistant conditions faced by nephrologists. While glucocorticoids have traditionally been the mainstay of initial treatment, they induce remission in only a minority of patients. A variety of other immunosuppressants have been utilized against steroid-resistant FSGS, but few have been rigorously examined in well-controlled trials. Recently, the results were published from a National Institutes of Health (NIH)-sponsored multicenter randomized trial comparing cyclosporine (CSA) with a combination of mycophenolate mofetil (MMF) and pulse dexamethasone (DEX) for the treatment of steroid-resistant FSGS. No difference in treatment effectiveness was shown between the two groups, and adverse effects were comparable. This was the largest randomized trial ever undertaken in FSGS, but it was unfortunately underpowered to show clinically relevant differences in response rates. This shortcoming, along with particularities of the study population and outcome measures, makes it challenging to draw definitive conclusions from the trial results. Despite these limitations, the trial does provide valuable insights into treatment strategies for FSGS and offers important lessons for planning future research.

INTRODUCTION

It is an oft-noted observation that nephrology suffers from a paucity of high-quality clinical trials, especially concerning the treatment of non-diabetic glomerular diseases [1–4]. A prime example of this is idiopathic focal segmental glomerulosclerosis (FSGS). The most commonly recommended initial treatment for this condition—glucocorticoids—has never been evaluated in a randomized controlled trial in adults [5, 6]. In the substantial proportion of patients resistant to glucocorticoids, several other immunosuppressants have been tried, mostly outside of randomized trials [5].

There are many reasons why idiopathic FSGS has been difficult to study in a randomized trial setting [1, 4, 7]. First, FSGS per se is not a single disease but a histologic expression of podocyte damage, which can be produced by a variety of distinct mechanisms including autoimmunity, genetic defects, infections, toxins or hemodynamic stress [7, 8]. Since the underlying mechanism is often difficult to determine with certainty, it may be challenging to recruit a sufficiently homogenous cohort of patients whose disease would be appropriately targeted by a given therapy, e.g. immunosuppression. A second related problem is that clinical presentations of FSGS vary in both children and adults, ranging from asymptomatic mild proteinuria to full-blown nephrotic syndrome, with variable severity and rapidity of renal failure [9, 10]. Third, many of the medications used for FSGS have substantial toxicity or a narrow therapeutic margin, making both recruitment and retention challenging. Fourth, while FSGS is relatively common for a glomerular disease, with a lifetime risk that may be on the order of 1 in 500 [11], the population prevalence is low enough that recruiting a large cohort of patients diagnosed early and willing to participate in research requires broad multicenter collaboration. This type of effort demands substantial logistic and financial support, which is unlikely to
be provided by the pharmaceutical industry, except for studying novel and patentable agents. Thus, a trial of off-patent immunosuppressants such as those commonly employed in FSGS almost inevitably requires government agency-funded sponsorship and coordination.

Against this background, the development of the National Institutes of Health (NIH)-sponsored FSGS clinical trial [12] comparing cyclosporine (CSA) with combined mycophenolate mofetil (MMF) and oral pulsed dexamethasone (DEX) was a noteworthy accomplishment. This multicenter randomized trial attempted to shed the light of evidence-based medicine on two readily available oral treatment regimens for steroid-resistant FSGS. Below, we discuss the basic approach to the therapy of FSGS, the conceptual basis for the NIH FSGS trial, its key features and findings and how the results should impact current practice.

Rationale for Treatment of FSGS

Idiopathic FSGS is one of the leading causes of end-stage renal disease (ESRD) in the United States [11]. Disease prognosis is closely predicted by the level and persistence of proteinuria. Patients with sustained non-nephrotic proteinuria have generally excellent outcomes, with kidney survival rates well over 90% after 5–10 years on conservative therapy alone [9, 10, 13, 14]. For nephrotic patients, the most important predictor of adverse outcomes is failure to achieve remission of proteinuria. While the best outcomes come with complete remission, even a partial remission (usually defined as a level of proteinuria below the threshold of the nephrotic range but above the threshold for macroalbuminuria, i.e. 0.3–3.5 g/24 h) confers markedly better prognosis than no remission [6, 10, 15–17]. With persistent nephrotic proteinuria, 5- and 10-year kidney survival rates are on the order of 65 and 35%, respectively, whereas achieving partial remission reduces the risk of ESRD by at least half [9, 10, 15]. Thus, to the degree that immunosuppressive treatment can induce a partial or complete remission, it should only be offered to patients with idiopathic FSGS and nephrotic-range proteinuria [18].

Glucocorticoids as Initial Therapy for FSGS

Traditionally, the initial therapy for idiopathic FSGS with nephrotic proteinuria has been a prolonged course of high-dose glucocorticoids. While there have been no randomized controlled trials evaluating this approach, a wealth of observational data have shown an association between glucocorticoid treatment and remission of proteinuria [10, 15–17, 19]. Glucocorticoids are cheap, effective immunosuppressants and their use in FSGS has been extrapolated from their success in childhood idiopathic nephrotic syndrome and adult minimal change disease. While various dosing schedules have been studied, a common high-dose algorithm is prednisone at 1 mg/kg of body weight daily or 2 mg/kg on alternate days [8, 18].

A key consideration in the use of glucocorticoids is appropriately defining treatment failure, or ‘steroid-resistance.’ This definition changes depending on the age of the patient, since children tend to respond to glucocorticoids more quickly than adults. The International Study of Kidney Disease in Children showed that of nephrotic patients under the age of 16 who underwent remission with prednisone, 93.8% did so by Week 4 of therapy and 100% after an additional 3 weeks [20]. Adults may require a much longer time to achieve remission, but those who will remit generally do so by 16 weeks [9, 10, 16, 17, 21]. While later responses do occur, these come at the price of prolonged exposure to glucocorticoids and their inherent risks [21]. Therefore, a reasonable definition of steroid resistance is a lack of response after 8 weeks of full-dose prednisone therapy for children or 16 weeks of full-dose therapy for adults, and this was the definition adopted by the recent Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines for glomerulonephritis [18]. A significant proportion of FSGS patients (40–70%) will be steroid-resistant, and as noted earlier, this portends a poor prognosis, especially if remission cannot subsequently be achieved through other means.

It is worth noting that this concept of prolonged glucocorticoid treatment leading to remissions must be tempered by the reality that a few patients do experience spontaneous remission [6, 9, 22–24]. While this rate may be only 3–11%, and includes partial remissions, the lack of randomized controlled data limits our ability to properly identify the proportion of patients benefiting from active therapy as opposed to ‘tincture of time.’ Furthermore, prolonged glucocorticoid therapy carries well-known and significant risks, including—but not limited to— infection, hyperglycemia, bone disease, mood instability, Cushing’s syndrome and cosmetic changes including permanent striae.

Non-Glucocorticoid Immunosuppressants for FSGS

For steroid-resistant FSGS patients, the best-validated treatment is CSA. At least two good-quality randomized controlled trials of adults have shown the superiority of CSA over no treatment or placebo in achieving reduction or remission of proteinuria [25, 26]. The largest and most rigorously conducted of these was organized by the North America Nephrotic Syndrome Study Group, and randomized 49 subjects with steroid-resistant FSGS to 26 weeks of treatment with CSA plus low-dose prednisone or placebo plus prednisone [26]. Partial or complete remission occurred by 26 weeks in 70% of the CSA + prednisone group versus just 4% of the placebo + prednisone group. Creatinine clearance was also better preserved in the CSA group. Relapses were common after remission, however, and 60% of remitters had relapsed by Week 78.

Observational studies of CSA in FSGS have largely supported the findings of the randomized trials [27–30], as have small trials of CSA in children [31, 32]. In summary, while initial response rates to CSA are fairly robust, the relapse rate...
is high. The risk of relapse can be partially attenuated by prolonging treatment (at least >12 months), but this approach carries a heightened risk of CSA-induced nephrotoxicity.

For the substantial proportion of patients treated with CSA who do not respond, who suffer complete relapse or who cannot tolerate the treatment, is there a clear next step in the therapeutic algorithm? The NIH FSGS clinical trial was designed in part to address this problem, and will be discussed below, but certainly prior to its publication the answer would have been a resounding ‘no.’ Many other agents have been utilized as third- and fourth-line treatments for this population of patients, and the results have been presented mostly in the context of case series, uncontrolled or nonrandomized studies, underpowered randomized trials, or conceptually flawed trials such as those including heterogeneous diseases or treatments [30, 33–36]. Among these, the calcineurin inhibitor tacrolimus has shown some promise in observational studies [37, 38] and appeared similarly efficacious to CSA in a small pediatric randomized trial [39]. As a calcineurin inhibitor, it would be expected to have similar practical limitations to CSA and does not offer a truly alternative approach. Other therapies reported with mixed results include alkylating agents, azathioprine, sirolimus and rituximab.

Mycophenolate represents a generally well-tolerated immunosuppressant with an alternate mechanism of action to the calcineurin inhibitors. Several uncontrolled trials of adults and children with FSGS treated with MMF with or without glucocorticoids have shown response rates of over 40% as defined by significant decreases in proteinuria [40–43]. In a randomized trial of adults with idiopathic nephrotic syndrome published in this journal in 2008, 33 subjects with FSGS were randomized to either MMF 2 g/day for 6 months + low-dose prednisolone 0.5 mg/kg/day for 2 to 3 months or to full-dose prednisolone 1 mg/kg/day for 3–6 months [44]. While the proportion of complete and partial remissions was similar in the two groups, the MMF group achieved remission more quickly (5.6 weeks versus 10.2 weeks) and received a lower cumulative prednisolone dose. In light of this and similar data, the NIH FSGS clinical trial was conceived to compare MMF and CSA.

**NIH FSGS CLINICAL TRIAL**

This multicenter, randomized controlled trial was an ambitious undertaking designed to directly compare two treatment regimens for FSGS on the background of standard therapy including low-dose prednisone: CSA, already established by randomized trials as an effective though imperfect therapy, and a combination of MMF and pulsed DEX, which was seen as an approach carrying a heightened risk of CSA-induced nephrotoxicity.

The central null hypothesis that the trial intended to test was that treatment with CSA would be equivalent to treatment with a combination of MMF–DEX in achieving remission of proteinuria for steroid-resistant adult and pediatric FSGS patients. This hypothesis ultimately was not rejected; that is, the trial did not detect a significant difference in outcomes between the two treatment arms. Such a ‘negative’ finding immediately prompts concern for the possibility of a type II (beta) error, i.e. that the trial failed to detect a true difference between the treatment arms. Careful analysis of the trial design and conduct is warranted to best assess the possibility of type II error, and also to understand how the findings should or should not be generalized to routine clinical practice.

**Study population**

The eligibility criteria for the trial were described in a separate manuscript [45]. Patients between the ages of 2 and 40 years with biopsy-proven FSGS were eligible if they had an estimated glomerular filtration rate (eGFR) of ≥40 mL/min/1.73 m² and urinary protein-to-creatinine ratio (Up/c) > 1 g/g, sustained over two visits. The subjects had to be steroid-resistant, which here was universally defined as Up/c > 1 g/g, despite a minimum of 4 weeks of high-dose glucocorticoids. A central pathology review was performed to ensure that biopsies were consistent with primary and not secondary FSGS, and obese subjects were excluded to limit the presence of obesity-associated FSGS.

Several points merit mention here. First, the proteinuria cutoff was quite low for a primary FSGS cohort treated with immunosuppressants. Indeed, the original recruitment plan had specified a cutoff of Up/c of 2 g/g, but this was lowered in an attempt to increase recruitment. Second, there were no eligibility requirements made regarding clinical or biochemical features of the nephrotic syndrome, such as edema, hypoalbuminemia or hyperlipidemia. Third, the definition of steroid resistance used (4 weeks), while probably appropriate for most children, would theoretically misclassify many steroid-sensitive adults as ‘steroid resistant’, since—as discussed earlier—adults often take much longer than 4 weeks to achieve steroid-induced remission.

The sum effect of these criteria was to boost recruitment in exchange for (i) increased disease heterogeneity of the study population, (ii) possible misclassification of steroid resistance according to the usual criteria and (iii) inclusion of subjects with relatively good prognosis (subnephrotic proteinuria and no nephrotic syndrome) who might not derive much benefit from immunosuppressant therapy. Indeed, 33 of 138 randomized subjects had baseline Up/c <2 g/g, and fully 50% of the subjects had Up/c <4 g/g. While none of these criteria should have favored one treatment arm over the other, they would cumulatively tend to decrease the treatment response rate, and therefore, bias the study as a whole towards a null outcome.

About one-third of the patients were aged 2–12 years, one-third aged 13–17 years and the final third aged 18+ years. Sex distribution was equal, and black race and Hispanic ethnicity were well represented. Baseline characteristics appeared mostly well balanced between the two groups. However, the MMF–DEX group had a higher number of subjects with tip-lesion histology (10 versus 4 in the CSA group), while fewer subjects with baseline Up/c <2 g/g (13 versus 20
in the CSA group). Since tip lesions tend to be a more treatment-sensitive entity [8], and since baseline subnephrotic proteinuria would less likely respond to immunosuppression, these differences theoretically could have increased the likelihood of treatment responses in the MMF–DEX arm.

**Design and interventions**

The trial was randomized but open-label, so subjects and their treating providers were aware to which arm each subject had been randomized. This introduces the possibility of bias from both providers and subjects, especially compliance and withdrawal bias. It is somewhat reassuring that the overall dropout rate was low, but there was a suggestion of uneven dropout with 6 subjects (9%) in the MMF–DEX arm missing follow-up visits compared with 15 (21%) in the CSA arm.

All enrolled patients were treated with low-dose prednisone (0.3 mg/kg every other day) for 6 months, and all patients were treated with lisinopril (or, if intolerant, losartan) at the maximally tolerated dose. In the CSA arm, dosage was adjusted to target a 12-h trough level of 100–250 ng/mL. In the MMF–DEX arm, MMF was dosed 25–36 mg/kg/day up to 2 g/day. DEX pulses were given weekly for the first 8 weeks, then biweekly until week 26, then every 4 weeks through Week 50. The decision to add pulsed DEX was based on the data showing good response rates to regimens of pulsed methylprednisolone added to alternate-day prednisone, with or without alkylating agents [46], as well as an unpublished study of pulsed DEX presented in abstract form by Smith et al. at the 2003 ASN meeting (abstract SA-PO1034, available at [www.asn-online.org/education_and_meetings/kidneyweek/archives/2003-abstracts-archive.pdf](https://academic.oup.com/ndt/article-abstract/28/3/527/1815080)).

**Power calculation and outcome measures**

The original power calculation had called for 500 subjects to be randomized in order to have 80% power to detect a roughly 10% absolute difference in remission at an alpha level of 0.05. In total, 138 subjects were actually randomized, which meant that for the same power and alpha level, the detectable difference would be about twice as large (~20%). Thus, the study was grossly underpowered to detect clinically important differences in efficacy between the two arms.

Partial remission was defined as a decrease in Up/c of at least 50% from baseline to a final value of 0.2–2 g/g. Complete remission was defined as sustained Up/c <0.2 g/g. In order to increase statistical power, the primary study outcome was defined by a complex six-level ordinal outcome variable, summarized in Table 1 (and presented graphically in the original manuscript). Essentially, the variable ranked complete and partial remissions between Weeks 26 and 52 in order from best to worst, with worse rank scores if a subject had a later response, experienced relapse or had no response at all. What would traditionally be considered favorable responses were classified from 1 (early and sustained complete remission) to 3 (partial remission achieved by Week 56), whereas outcomes 4, 5 and 6 involved relapse of proteinuria or no response. The main secondary outcome was a similar multilevel ordinal variable characterizing the maintenance of remission from Weeks 52 to 78.

**Table 1. Ordinal classification of the primary outcome in the FSGS clinical trial**

<table>
<thead>
<tr>
<th>Primary Outcome</th>
<th>Disease status by proteinuria</th>
<th>Week 26</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>PR or CR</td>
<td>PR</td>
<td>Relapse</td>
</tr>
<tr>
<td>4</td>
<td>PR or CR, then relapse by Week 26</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>No remission</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CR, complete remission, defined as Up/c <0.2 g/g; PR, partial remission, defined as Up/c reduction >50% from baseline to a final value of 0.2–2 g/g.

Tables 2 and 3 summarize the results of the primary and secondary outcomes. Table 3 focuses specifically on the Week 78 outcomes for those patients who had been in either complete or partial remission at Week 52. While no differences were statistically significant, point estimates for every level of the primary outcome favored CSA. Pre-specified subgroup analyses did not suggest discrepancies in response to treatment across age, race, baseline Up/c, baseline eGFR or previous steroid exposure. Additional analyses were done to examine changes in Up/c and eGFR over time. Proteinuria decreased in both groups, but to a greater extent in the CSA group. At Week 26, the median ratio of proteinuria compared with baseline (25th–75th percentiles) in the CSA group was 0.24 (0.10–0.54) versus in the MMF–DEX group 0.46 (0.25–0.81) (P = 0.039). Conversely, the CSA group experienced a greater decline in eGFR at Week 26, with ratio 0.73 (0.63–0.89) compared with MMF–DEX 0.95 (0.79–1.14) (P = 0.001). Adverse event rates were similar in the two groups, and the key events are summarized in Table 4.

**DISCUSSION**

The NIH FSGS clinical trial is by some margin the largest randomized trial ever carried out for steroid-resistant FSGS, and indeed among the largest trials for any glomerular disease outside of diabetic nephropathy or lupus nephritis. The study participants represent a broad swath of FSGS in the United States; they were randomized at over 50 centers across the country, and made up a heterogeneous group with strong representation from racial and ethnic minorities. The one caveat is that this was a largely pediatric FSGS population, with two-thirds of the cohort younger than 18. Overall response to therapy was moderate, with 40% of patients in both groups achieving complete or partial remission after 1 year, and only 60% of those (24% of the total) still in
remission 6 months later. This highlights the morbidity and treatment resistance of FSGS.

While the study population was demographically diverse, there are reasonable concerns that it may have been contaminated by subjects with secondary or genetic forms of FSGS. As discussed above, the eligibility criteria allowed recruitment of patients with relatively low urine protein excretions and did not consider clinical features that might suggest secondary forms, such as lack of full nephrotic syndrome. Conversely, the strength of the study was the centralized biopsy review with attention to ruling out secondary forms, and the exclusion of obese patients. The lack of formalized genetic testing to determine the eligibility criteria may be seen as a weakness, although it represents typical real-world clinical practice. The results from genetic studies of the cohort are expected to be published in ancillary reports, and should help clarify the prevalence and significance of genetic mutations in these patients. Overall, the potential inclusion of subjects with secondary or genetic forms of FSGS would be expected to result in a lower response to treatment in both the arms, and therefore, bias the trial towards a null result.

The main conclusion of the study was that there was no statistical difference in response rates for proteinuria in steroid-resistant FSGS between CSA and combined MMF–DEX. This should not be interpreted as a statement of equivalence between these two regimens. Unfortunately, the study was largely underpowered to discover clinically important differences in response rates between the treatments, raising the possibility of a substantial type II (beta) error. This lack of power was reflected by the wide confidence interval of the odds ratio for the primary outcome. This confidence interval, despite crossing unity, was mostly distributed across a range of values that favored CSA. This is all the more notable because if anything, there were reasons to predict that the

Table 2. Summary of the primary outcome of the NIH FSGS clinical trial: complete or partial remissions in Weeks 26–52.

<table>
<thead>
<tr>
<th>Primary outcome level</th>
<th>Outcome frequency</th>
<th>Cumulative OR for a given outcome level or better</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMF–DEX (n = 66)</td>
<td>CSA (n = 72)</td>
</tr>
<tr>
<td>1 (CR at 26 weeks)</td>
<td>2 (3.0)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>2 (CR at 52 weeks)</td>
<td>4 (6.1)</td>
<td>10 (13.9)</td>
</tr>
<tr>
<td>3 (PR at 52 weeks)</td>
<td>16 (24.2)</td>
<td>19 (26.4)</td>
</tr>
<tr>
<td>All CR + PR</td>
<td>22 (33.3)</td>
<td>33 (45.8)</td>
</tr>
</tbody>
</table>

CR, complete remission; PR, partial remission; OR, odds ratio; CI, confidence interval.
Adapted from Table 2 of Gibson et al. [12].

Table 3. Summary of the secondary outcome of the NIH FSGS clinical trial: remission status at Week 78 among patients who had at least partial remission at Week 52.

<table>
<thead>
<tr>
<th>Secondary Outcome Level</th>
<th>Outcome frequency</th>
<th>MMF–DEX (n = 22)</th>
<th>CSA (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>4 (18%)</td>
<td>11 (33%)</td>
<td></td>
</tr>
<tr>
<td>At least partial remission</td>
<td>17 (77%)</td>
<td>16 (48%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (5%)</td>
<td>6 (18%)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Table 3 of Gibson et al. [12].

Table 4. Summary of important adverse events at Week 52a

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>MMF–DEX (%)</th>
<th>CSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious infection requiring hospitalization</td>
<td>13.6</td>
<td>9.7</td>
</tr>
<tr>
<td>Serious cardiovascular event</td>
<td>1.5</td>
<td>0</td>
</tr>
<tr>
<td>Hospitalization for any reason</td>
<td>27.3</td>
<td>23.6</td>
</tr>
<tr>
<td>Death</td>
<td>3.0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>74.2</td>
<td>69.4</td>
</tr>
<tr>
<td>Infection, any</td>
<td>45.5</td>
<td>40.3</td>
</tr>
</tbody>
</table>

All numbers reported are percentages.
Adapted from Table 4 of Gibson et al. [12].

aSubjects censored at Week 26 due to treatment failure could not subsequently contribute to adverse events from Weeks 26–52.
MMF–DEX group in this study might have had a superior remission rate for reasons separate from the specific drug efficacy. These reasons include the aforementioned greater number of tip lesions, lower number of subjects with Up/c <2 g/g and the use of pulse DEX therapy for a study population that was probably not universally steroid-resistant (especially the adults).

We believe that CSA remains the first-line therapy for steroid-resistant FSGS, in accordance with the recently published KDIGO clinical practice guidelines for glomerulonephritis [18]. However, the NIH FSGS clinical trial produced several other useful insights into the treatment of FSGS. First, while we cannot conclude that MMF–DEX is equivalent to CSA, and in fact, should retain suspicion that it may be inferior for achieving proteinuria remission, it is certainly a reasonably effective and acceptably tolerated regimen for patients unable to tolerate CSA or who have failed to respond to CSA. Furthermore, the NIH FSGS trial, like many other trials in nephrotic syndrome, used a primary outcome based on proteinuria, a surrogate outcome. The fact that the eGFR trended down in the CSA group, while it appeared to be relatively preserved in the MMF/DEX group, raises concern that we may be neglecting the crucial long-term ‘hard’ outcomes of kidney survival and patient survival. For now, special consideration should be given for MMF–DEX in patients with baseline-impaired GFRs, with declining GFRs on a calcineurin inhibitor, or in those who achieve remission but then become dependent on immunosuppression to maintain remission, and who are therefore faced with the prospect of prolonged therapy even after a year.

What does the NIH FSGS clinical trial mean for future research endeavors into improving the treatment of FSGS? First, despite the trial falling far short of recruitment goals and therefore suffering the power limitations noted above, it remains a very large trial for this field, with an unprecedented breadth of collaboration involved in recruiting patients. In this sense, it represents a successful model of collaboration that can be scaled upwards and improved by future efforts. It also highlights a particular challenge of studying and treating FSGS. As currently defined by histology, FSGS is a clinically heterogeneous disease. Trial recruitment criteria can be manipulated to include a more or less heterogeneous population, but even the strictest criteria will include patients with variable treatment sensitivity and prognosis. A large proportion of treated subjects will be exposed to toxic medications without any clinical benefit. It is our hope that the use of emerging biomarkers, as well as genomic and proteomic techniques, will allow future researchers and clinicians to identify specifically active mechanisms of disease for any given patient, and thereby offer tailored, personalized therapy that maximizes efficacy while minimizing risk [7, 47].

**CONCLUSIONS**

The NIH FSGS clinical trial remains a landmark study in the field of glomerular disease for its scope and breadth, and the study investigators are to be commended for coordinating and carrying out such an immense undertaking. Despite their best efforts, the trial remained grossly underpowered, which in turn forced several methodological sacrifices to be made in order to maximize enrollment. This is a failure not of the investigators, but of the clinical nephrology community as a whole, who owe it to our patients to engage them in research, enroll them in studies and allow more of these types of investigations to be done.

Finally, in discussing the intricacies of this study, we cannot forget to point out an ‘elephant in the room’ of treating idiopathic FSGS, which is that the ‘state-of-the-art’ therapies remain distressingly rudimentary. Our understanding of disease mechanisms is still poor, and in broadly applying toxic and nonspecific immunosuppressants we are undoubtedly harming a large number of patients who do not stand to benefit from them. A clearer understanding of underlying disease mechanisms, better targeted therapies and more discriminatory methods of predicting treatment responsiveness is urgently required.

**CONFLICT OF INTEREST STATEMENT**

None declared. The content presented in this paper has not been published previously in whole or part.

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Sailing between Scylla and Charybdis: oral long-term anticoagulation in dialysis patients

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ABSTRACT

End-stage renal disease (ESRD) patients exhibit an increased risk of bleeding compared with non-chronic kidney disease (CKD) patients due to uraemic platelet dysfunction, altered vessel architecture and other factors. This renders any long-term oral anticoagulation potentially difficult. While there is little doubt that ESRD patients with recurrent thromboembolism or a mechanical cardiac valve should receive vitamin K antagonists (coumarins), the use of coumarins in ESRD patients with atrial fibrillation is a matter of debate. In non-CKD patients, current guidelines strongly recommend the use of oral anticoagulants for stroke prophylaxis in atrial fibrillation if certain risk factors are present (CHA2DS2-VASc score). This recommendation is often extrapolated to patients with advanced CKD or ESRD but data supporting this practice are weak to absent. Besides an increased bleeding risk in ESRD patients, coumarins will also accelerate cardiovascular calcification and are potent risk factors for the development of calcific uraemic arteriolopathy (calciphylaxis). Novel coumarin alternatives such as direct thrombin inhibitors are promising but none is currently approved for use in ESRD patients. Whether interventional treatment strategies such as atrial appendage occlusion are safe and effective options in advanced CKD is also as yet unresolved. This review attempts to balance the potential risks and benefits of coumarin usage in ESRD patients and to give the best possible recommendations for everyday patient care.

RISK OF HAEMORRHAGE IN HD PATIENTS

Patients on haemodialysis (HD) carry a significantly increased bleeding risk [1, 2]. Depending on the cohorts investigated, previous data describe a 1.4- to 5.2-fold increase in the relative risk for gastrointestinal bleeding [3, 4] and an ~6–10 times higher incidence of intracerebral bleeding in end-stage renal disease (ESRD) patients compared with non-renal patients [5, 6]. The reasons for this increased bleeding risk are multifactorial, in part related to uraemia, such as decreasing platelet aggregation and increasing bleeding time. The latter may be linked to uraemic toxins [7] and impaired nitric oxide metabolism [8].

INDICATIONS AND CONTRAINDICATIONS FOR LONG-TERM ANTICOAGULATION IN PATIENTS ON DIALYSIS

Several clinical scenarios require long-term oral anticoagulation treatment (OAT) in both the general population as well as in patients with chronic kidney disease (CKD) and ESRD (see below). In the general population, atrial fibrillation also requires long-term OAT therapy, if certain risk factors are