Treatment of primary focal segmental glomerulosclerosis

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Introduction

Focal segmental glomerulosclerosis (FSGS) is just one of several deceptive denominations for a glomerulopathy that in fact is a podocyte disease [1]. A host of conditions are liable to injure the glomerular epithelial cells and lead to FSGS [2]. Therefore, it should be stressed that FSGS is a lesion, not a disease. From this standpoint, the topic ‘Treatment of FSGS’ may be considered a misnomer, as the podocyte disease that is the initial event in the natural history of FSGS is rarely, if ever, accessible to specific treatment. Once this initial cellular insult has led to the focal and segmental glomerular lesions, the goal of treatment is essentially to control proteinuria and hopefully to arrest or slow the development of glomerular fibrosis in order to limit progression to end-stage renal failure (ESRF).

Here we shall distinguish non-nephrotic from nephrotic primary FSGS, focusing mainly on the latter.

FSGS: description and natural history

The pathological description of FSGS has evolved over the years. Conventional descriptions refer to lesions initially localized within segments of the glomerular tuft lobules. Pathological variants include hilar, peripheral and glomerular tip lesions [3], and some publications contend that some of these localizations entail better prognosis than others, which has not been confirmed [4]. Recent histological techniques of three-dimensional (3-D) glomerular reconstruction have shed new light on the concept of ‘focal’ and ‘segmental’ sclerosis. Fuiano et al. [5] have shown by 3-D reconstruction that the glomerular lesions of FSGS are more widely distributed in the glomerular tufts than determined by conventional 2-D microscopy, and proposed to change the term ‘FSGS’ to ‘DSGS, diffuse segmental glomerulosclerosis’. Using the same approach, Fogo et al. [6] found that on initial section, the percentage of sclerosis was 31.5 ± 6.8% in adults vs 11.7 ± 5.7% in children. After serial section analysis, the difference was greater, with a figure of 48.0 ± 6.6% in adults, contrasting with 23.2 ± 7.4% in children, in whom focal lesions were smaller, more segmental and peripheral. Such findings might indicate that FSGS is not exactly the same condition according to age, which might explain differences in response to treatment.

The clinical picture of FSGS comprises two forms that apparently correspond to different entities. The first is characterized by insidious onset of low-grade proteinuria not reaching nephrotic levels. In a series of 492 adult cases, Korbet et al. [7] identified 32% of cases with this presenting feature of FSGS. The development of this form is slow and, in our experience, proceeds for decades before it leads to ESRF. The second form, which represents two-thirds of cases, is marked by a rapid or even sudden onset of a full-blown picture of nephrotic syndrome. Initial renal biopsy usually finds lesions of FSGS, but the glomeruli may be normal by light microscopy and immunofluorescence, leading to the misdiagnosis of minimal change disease. Resistance to corticosteroid therapy should suggest performing a repeat renal biopsy after completing an adequate course of treatment. In most cases, repeat biopsy discloses transition from minimal changes to FSGS [8], an ominous finding concerning further prognosis, as indicated below. Conversely, in some rapidly developing forms of nephrotic FSGS, severe cellular lesions of collapsing glomerulopathy are found in most but not all glomeruli. It has been shown recently that in these cellular variants of FSGS, podocytes undergo a process of cell transdifferentiation, losing their normal phenotype and expressing macrophagic markers [9].

Treatment of non-nephrotic FSGS is not codified. The absence of nephrotic syndrome and slow development, in addition to ignorance of pathophysiology, might explain this lack of information in the medical literature. However, non-nephrotic FSGS certainly excludes an aggressive therapeutic approach based on corticosteroids or any form of immunosuppressive regimen. Conservative treatment should consist of dietary measures aimed at reducing overweight, controlling hyperlipidaemia, when present, and normalizing blood pressure with angiotensin-converting enzyme (ACE) inhibitors. Whether AT1 antagonists are endowed with...
comparable efficacy on proteinuria remains to be determined.

Importance of affirmative treatment of nephrotic FSGS

It was long considered that nephrotic syndrome complicating FSGS was corticosteroid resistant. In a review of the literature totalling 153 adult cases published between 1961 and 1986, we found that the response rate to corticosteroids was 15.6% complete remission, 20.2% partial remission and 59% failure. However, contrary to paediatricians who apply codified treatment schedules to nephrotic children [11–16], most publications dealing with treatment in adults before 1986 reported on short series of patients and various regimens of corticosteroids, in terms of both dosage and length of treatment.

In 1987, Pei et al. [17] pointed out that the poor prognosis of nephrotic FSGS essentially stemmed from undertreatment. Undertreatment was explained by the conviction on the part of most nephrologists that treatment was of no avail. In cases where treatment was given, courses were often too short to obtain remission. In fact, it appeared [7] that when nephrologists caring for adults applied the 6 week corticosteroid schedule recommended by paediatricians, the response rate was of the order of 20%, whereas when duration of therapy was >5 months, the rate of complete remission rose above 30%. During the last decade, several publications contributed to design treatment protocols of nephrotic FSGS in adults and children that improved the remission rate and favourably influenced the development to renal failure in this condition.

Corticosteroid therapy

Corticosteroids, essentially prednisone or prednisolone, remain the mainstay of treatment in idiopathic nephrotic syndrome, including FSGS. Dr Korbet, in another contribution in this issue, clearly shows that pushing a nephrotic patient into remission has a paramount value for predicting reduced risk of development to chronic renal failure. That a positive response to corticosteroid treatment just selects patients who in any case would have fared better than their steroid-resistant fellow sufferers is not a convincing hypothesis, considering the poor renal survival rate of patients who remain nephrotic throughout the course of their disease.

Corticosteroid treatment of childhood nephrotic FSGS has long been codified by paediatricians [14,18]. Prednisone is prescribed at a dosage of 60 mg/m²/day for an average of 6 weeks. Paediatricians pronounce corticosteroid resistance when remission is not obtained after 1 month of full-dose treatment followed by three pulses of methylprednisolone, 1 g/1.73 m². Early non-responders represent 6% of nephrotic children [19]. However, two-thirds end up as responders and only one-third remain non-responders.

Recently, the American paediatric nephrologists Tune and Mendoza [20,21] devised an aggressive therapeutic protocol based on high-dose methylprednisolone and prednisone, administered for a total of 82 weeks (see Table 1). They obtained a high rate of remission in steroid-resistant nephrosis with surprisingly few side effects. This protocol seems to be regarded with some reserve in Europe.

The response of adults to corticosteroids is much slower than in children. This is true in minimal change disease and all the more so in FSGS. Contrary to the situation in children, corticosteroid resistance should not be pronounced before a 4 month course of full-dose prednisone (1 mg/kg/day) has been completed [22]. Korbet et al. [7,22] analysed the initial response to treatment in adults with FSGS before and since 1980. The results are shown in Table 2. The dosage of prednisone ranged from 0.5 to 2 mg/kg/day. However, the highest complete remission rates, >30%, were observed in cases treated for >5 months, and the lowest, ≤20%, in patients treated for ≤2 months. A suggested schedule for treating an adult with nephrotic syndrome and lesions of FSGS is the following [23]: prednisone 1 mg/kg/day (up to 80 mg/day) for 8–12 weeks, followed by 0.5 mg/kg/day (or 60 mg every other day) for 6–8 weeks, then tapering to a stop over 8 weeks. If remission, or significant reduction of proteinuria along with an increase in serum albumin, is not obtained at 8 weeks, the initial full-dose treatment can be prolonged to 16 weeks. It is possible that a longer course of high-dose corticosteroid treatment might lead to a few more cases of remission, but the therapeutic hazards, including diabetes and hip

### Table 1. The 'Mendoza' protocol for treating corticosteroid-resistant idiopathic nephrotic syndrome in children

<table>
<thead>
<tr>
<th>Week</th>
<th>Methylprednisolone 30 mg/kg</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>Three times/week</td>
<td>None</td>
</tr>
<tr>
<td>3–10</td>
<td>Every week</td>
<td>2 mg/kg qod</td>
</tr>
<tr>
<td>11–18</td>
<td>Every 2 weeks</td>
<td>With/without taper</td>
</tr>
<tr>
<td>19–50</td>
<td>Every 4 weeks</td>
<td>Slow taper</td>
</tr>
<tr>
<td>51–82</td>
<td>Every 8 weeks</td>
<td>Slow taper</td>
</tr>
</tbody>
</table>

Source: ref. 20.

### Table 2. Response to initial corticosteroid treatment in adults with FSGS

<table>
<thead>
<tr>
<th></th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>265</td>
<td>35</td>
<td>13</td>
</tr>
<tr>
<td>&lt;1980</td>
<td>127</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>&gt;1980</td>
<td>138</td>
<td>47</td>
<td>8</td>
</tr>
</tbody>
</table>

Figures are given as percentages (source: ref. 22).
osteonecrosis, increase to such an extent that this option should be discouraged strongly. However, given that an abrupt stop of corticosteroid treatment entails a definite risk of rebound effect with flare-up of nephrotic syndrome, it is advisable to taper corticosteroid dosage over an additional 3 months. This period of tapering is in fact critical, as a minority of patients with nephrotic FSGS achieve complete and stable remission after tapering corticosteroids to a stop. Most are corticosteroid-dependent, some of them to a high threshold dose. Pursuing indefinite treatment with a maintenance dosage of steroids invariably leads to steroid toxicity, as illustrated in Figure 1.

Corticosteroid resistance as well as corticosteroid dependency justify the trial of other therapeutic agents, essentially cytotoxic therapy and cyclosporin A.

**Alkylating agents**

Alkylating agents have been used in the treatment of idiopathic nephrotic syndrome since 1949. The two agents most commonly used are cyclophosphamide and chlorambucil. Their best indication is corticosteroid-sensitive, but multirelapsing, nephrotic syndrome with minimal glomerular lesions, i.e. no focal sclerosis. Unfortunately, this is not the usual course of nephrotic FSGS, where, in cases of corticosteroid sensitivity, steroid dependency is the rule and multiple relapses the exception. In any event, indications for treating nephrotic FSGS with alkylating agents are corticosteroid resistance and corticosteroid dependency. It is difficult to determine the respective efficacy of cytotoxic drugs in these two subsets, as data in the literature usually indicate the results of the first course of such drugs and very rarely provide longitudinal studies.

A rough idea, however, can be drawn from some retrospective publications [7,10]. The main predictor of efficacy is the initial response to steroids. In steroid-responsive cases, the rate of complete remission, partial remission and failure is of the order of 50, 25 and 25%, respectively of the cases. Conversely, steroid resistance is highly predictive of resistance to cytotoxic agents, with the corresponding figures of ~10, 10 and 80%.

In children, the Arbeitsgemeinschaft für Pädiatrische Nephrologie determined that a 12 week course of cyclophosphamide using a dosage of 2 mg/kg/day is clearly superior to an 8 week course [11]. Longer periods of treatment or higher dosages are not superior in terms of efficacy and increase the risk of toxicity. The same holds true for adults. In both adults and children, it is common practice to add a maintenance dosage of steroids to the cytotoxic drugs in the hope of increasing efficacy.

**Azathioprine**

There are few data regarding the efficacy of azathioprine in idiopathic nephrotic syndrome. In 1974, Linshaw and Gruskin, on behalf of the ISKDC [24], concluded on the inefficacy of this antimetabolite in children. Occasional publications gave contradictory results, but especially in minimal change disease [10,25]. However, Cade et al. [26] in 1986 indicated that they had treated with azathioprine, at a dosage of 2–2.5 mg/kg/day, 13 adults with idiopathic nephrotic syndrome, including five with FSGS. At 24 months, 12 patients who were still followed up were in complete remission. To the best of our knowledge, no large-scale trial of treatment with a long course of azathioprine has since been published, and this is obviously regrettable, considering the relatively good tolerance of this drug compared with that of alkylating agents.

**Cyclosporin A**

The first trials of cyclosporin A (CsA) treatment of idiopathic nephrotic syndrome were reported in 1986 [27]. Present experience amounts to thousands of patients reported in a host of publications [28], all concurring that the best results of CsA treatment are achieved in corticosteroid-sensitive cases, including responders and multirelapasers. Unfortunately, as stated above, the usual course of nephrotic FSGS is characterized by steroid resistance, less often steroid dependency and very rarely multiple relapses. It follows that the results of CsA treatment are mostly disappointing in this subset of idiopathic nephrotic syndrome. In addition, even in cases of complete or partial success of CsA treatment, attempts to taper this regimen to a stop are followed almost invariably by relapse of nephrotic syndrome, indicating cyclosporin dependency with the attending hazards of declining renal function, owing to the nephrotoxic effects of the drug.

![Fig. 1. Patient with profuse proteinuria, nephrotic syndrome and glomerular lesions of focal segmental glomerulosclerosis. Treatment with prednisone was started at a dosage of 1 mg/kg/day. Slow partial remission was obtained at 4 months. Prednisone dosage was tapered but, when it reached 15 mg/day, proteinuria increased and oedema reappeared. Nephrotic syndrome was controlled by increasing the dosage to 20 mg/day, obtaining 24 h proteinuria levels of the order of 3 g. After 2 years of such treatment, the patient, who was mildly Cushingoid, complained of hip pain. Magnetic resonance examination disclosed bilateral severe hip osteonecrosis requiring hip replacement. This case illustrates the trade off between a 'favourable response' to treatment and its complications.](image-url)
In children, Niaudet and Habib [29] reviewed eight studies involving 60 steroid-resistant patients. Complete remission was obtained in only 20%. Given the poor results of CsA therapy and evidence of nephrotoxicity on repeat renal biopsy, Melocoton et al. [30] expressed reservations concerning both the efficacy and safety of this treatment. However, Niaudet et al. [31] analysed the results of a combination of CsA and prednisone in 65 children treated for 5 months. A total of 42% went into complete remission and 6% into partial remission. Considering the poor prognosis of steroid-resistant idiopathic nephrotic syndrome, these results of combined steroid and CsA treatment are rather encouraging. However, this should not obscure the fact that cyclosporin is nephrotoxic. Niaudet [32] and Melocoton [30] carried out serial renal biopsies in children so treated whose renal function, assessed by serum creatinine, was apparently stable. They showed that this apparent stability was falsely reassuring, as serial renal biopsies disclosed increasing interstitial fibrosis.

The results of CsA treatment in adults were reviewed in 1995 in Europe [28] and in America [22]. The French collaborative group of the Société de Néphrologie enrolled 46 patients with nephrotic FSGS. Eleven (24%) underwent remission and 35 (76%) failed to respond. The lowest response rate was observed in steroid-resistant forms (20%). In the experience of Ponticelli et al. [33], including 10 adult patients with FSGS, partial remission was obtained in seven and three were failures. However, outcome at discontinuation at month 12 was complete remission in one patient and the nine others were nephrotic.

Time to remission was analysed by the Collaborative Study Group of Sandimmun in Nephrotic Syndrome [34]. The maximum cumulative rate of complete remission was achieved at 6 months, indicating that pursuing CsA treatment for a longer period of time is of no avail in terms of additional remissions, whilst entailing an unreasonable risk of nephrotoxicity.

In fact, renal toxicity is the major concern in the treatment of idiopathic nephrotic syndrome and especially in the case of glomerular lesions of FSGS. Meyrier et al. [35] studied renal tolerance of CsA treatment in 14 cases of nephrotic FSGS in whom repeat renal biopsy was carried out after 19.6±15.2 months of treatment with a dosage of 5.54±0.81 mg/kg/day. In nine cases, CsA treatment had to be stopped for failure and/or rapidly progressing renal insufficiency. Interstitial fibrosis was already present before CsA treatment, a common observation in FSGS. Fibrosis increased in all patients. Aggravation of interstitial fibrosis along with developing glomerular lesions of FSGS was observed in some cases in which CsA had led to partial or even complete remission.

Similarly to corticosteroids and alkylating agents, treatment of nephrotic FSGS with cyclosporin faces the clinical nephrologist with the dilemma of making a choice between the devil and the deep blue sea. Despite the foregoing data on CsA nephrotoxicity, the drug pushes to complete plus partial remission ~30% of patients who were stubbornly resistant to other treatments. Given the hazards of the nephrotic state, and despite the risk of faster development of renal insufficiency, one-third of the patients benefit from a period of clinical improvement. On ethical grounds, these aspects of the treatment must be discussed frankly with the patient, with clear explanations on the pros and cons of this and other forms of immunosuppressive therapy.

**Other drugs**

McCauley et al. [36] published the results of a trial of FK506 which included four children with FSGS. Proteinuria significantly declined but, as with cyclosporin, Tacrolimus induced a rapid increase in serum creatinine. In addition, attempts to taper the drug to a stop were followed by relapse of nephrotic syndrome, indicating dependency on the drug. Recently Briggs et al. [37] reported on eight cases of glomerular disease treated with mycophenolate mofetil, including one with FSGS. This patient was proteinuric but not nephrotic and had a mild degree of renal insufficiency. The result of this treatment was not very convincing.

**Relapse on transplanted kidney**

Relapse of nephrotic syndrome and glomerular lesions is observed in 30% of patients undergoing renal transplantation. In 25% of cases, such recurrence leads to loss of the transplanted kidney and return to dialysis [38]. In some reports [39], increased immunosuppressive dosage and repeated sessions of plasmapheresis seemed to have partially controlled an unfavourable evolution. Another approach, similarly aimed at removing the unknown circulating factor which causes both proteinuria and FSGS [40], has been plasma protein adsorption on columns coated with staphylococcal protein A [41]. The benefits of such experimental procedures were of relatively short duration.

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**References**