

Focal segmental glomerulosclerosis: treatment with steroids

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GUIDELINES

While remission may be induced in patients receiving steroids, there have been no level I or II studies confirming the efficacy of this intervention in the preservation of renal function in adults with primary focal segmental glomerulosclerosis (FSGS)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **It is uncommon for patients with normal renal function and non-nephrotic proteinuria to progress to renal impairment. Consequently, steroid therapy in these patients is currently unjustified. Nonetheless, supportive therapy including aggressive control of blood pressure and dyslipidemia and blockade of the renin angiotensin system would seem prudent. In addition, long-term follow-up is still required to monitor for the development of adverse indicators including nephrotic range proteinuria and hypertension that could presage a more progressive course. (Level IV evidence)**
- **Some studies have shown that, independent of the degree of proteinuria, patients with renal dysfunction and/or interstitial fibrosis have a significantly decreased renal survival. (Level III evidence) This has led some to consider a trial of steroids in FSGS with renal impairment and non-nephrotic proteinuria in an attempt to induce remission. However, there are currently no studies to support this practice. In addition, nephrotic patients with renal dysfunction or interstitial fibrosis tend to be less responsive to therapy (Korbet et al 1994). At least some of these patients have secondary FGS (see guideline titled “FSGS: cytotoxic therapy”).**
- **Because of the desire to induce remission in patients with FGS and nephrotic range proteinuria, it has been suggested that a 6-month trial of steroid therapy may be useful. Certainly, a prolonged course of steroids (using prednisone doses of 0.5–2 mg / kg / day) can induce remission in between 30–60% of patients (Trojanov et al 2005, Pei et al 1987, Nagai et al 1994, Korbet et al 1994, Banfi et al 1991, Agarwal et al 1993, Rydel et al 1995, Miyata et al 1986, Detwiler et al 1994, Ponticelli et al 1999). However, this intervention has not been tested in any randomized controlled trial (RCT), making the accurate interpretation of the utility of**

steroid therapy problematic. Moreover, many series of patients with nephrotic syndrome have included an unknown number of patients with steroid-reversible nephropathy apart from FSGS, including minimal change disease.

- The Regional Glomerulonephritis Registry Study (Pei et al 1987) prospectively followed 95 adult and paediatric patients with biopsy-proven FSGS, for a mean of 61 months from the time of biopsy. The probability of remission with a long duration of therapy with corticosteroids (with or without cytotoxic drugs) was similar in adults (39%) and children (44%) with FSGS.
- Pei et al (1987) also found remission could be induced with steroid therapy in older patients (more than 60 years of age) with FSGS. In this study, 4 of the 9 patients (44%) who received treatment with prednisone achieved complete remission for a median duration of treatment of 6 months, alone or combined with cytotoxic therapy. There were no relapses in those patients who achieved remission and none progressed to renal failure. No untreated patients had a remission and 9 of the 14 untreated or non-responders progressed. Ninety-six per cent of the patients who had a complete remission had preservation of renal function, whereas the probability of end-stage kidney disease (ESKD) was 45% in those who had not responded or who were not treated. Treatment with steroids may be effective in preserving filtration function in children with FSGS with heavy proteinuria (> 3 g/day). (Level II evidence)
- At least 7% of the children enrolled in the International Study of Kidney Diseases has FSGS (ISKDC) [Pei et al 1987]. In this study, children were given daily corticosteroids in a dose of 60 mg/d/m² (up to 80 mg/d) for 4 weeks followed by 40 mg/d/m² given on three consecutive days out of seven for 4 weeks and then tapered off over 4 more weeks. Many children developed remission, although many others had remission without a diagnosis of FSGS ever being made. Conclusions about the efficacy of comparative steroids in FSGS are difficult to make in the context of this study. Nonetheless, this regimen has become the standard treatment for childhood nephritic syndrome.
- Korbet, Schwartz and Lewis (1994) reported a 50% response rate in a study of 16 adult patients with nephrotic syndrome and FSGS. Treatment consisted of 60 mg/day of prednisone for at least 1 month. Responses occurred by an average of 3.75 months (range: 1–10 months), and complete remission occurred at 5.75–6.75 months in the three patients who had complete remission. .
- Banfi et al (1991) retrospectively reviewed the management of 59 patients with FSGS and nephrotic syndrome treated with corticosteroids and/or immunosuppressive drugs. Twenty-seven patients were initially treated with corticosteroids alone for 9.3 months; 19 patients received corticosteroids and immunosuppressive agents associated or every other month for 5.5 months; 13 patients received either azathioprine or

cyclophosphamide alone for 25 months. At follow-up, 60% of patients had experienced complete or partial remission, most commonly after at least 8 weeks of treatment.

- Agarwal et al (1993) followed 38 adult cases with biopsy-proven FSGS and nephrotic syndrome treated with prednisolone; 58% showed response (31% complete remission and 27% partial remission). ·
- Rydel et al (1995) reported a retrospective assessment of 60 patients with nephrotic syndrome and FSGS. Thirty patients received prednisone, at a total dose of more than 60 mg/day for a minimum of 2 months, followed by a tapering schedule over 5–6 months. Fifteen patients (50%) achieved a remission by 3.7 months (10 complete remission and 5 partial remissions), with all patients responding within 9 months. Remission was more common in patients who received a dose of 60 mg/day or more of prednisone for a longer period of time. ·
- Miyata et al (1986) reviewed 32 patients with nephrotic syndrome due to FSGS treated with steroids alone. Forty-four per cent had complete remission, 12% partial remission and 44% no response. ·
- Ponticelli et al (1999) reviewed 80 nephrotic adults with FSGS and plasma creatinine lower than 3 mg/dL. Patients were given corticosteroids (53 patients) or immunosuppressive agents (27 patients) for a median of 16 and 75 weeks, respectively. Forty-two patients responded with complete remission (29 patients, 36%) or partial remission (13 patients, 16%). Twenty-six patients who did not respond were treated again. Two patients obtained complete remission and 13 a partial remission. Overall, 70% of nephrotic adults with FSGS obtained complete or partial remission and maintained stable renal function for about 10 years when given a prolonged therapy with corticosteroids or immunosuppressive drugs. · Patients with collapsing glomerulopathy, a more rapidly progressive form of FSGS, were less responsive to steroids, if at all.
- Valeri et al (1996) reviewed their experience with 43 patients with collapsing FSGS and found that none of the 26 patients benefited from treatment with prednisone alone. ·

Some studies have suggested that patients with a glomerular tip lesion associated with FSGS may be more likely to respond to steroid therapy, than those with typical sclerosis or collapsing glomerulopathy (Hogan-Moulton et al 1997, Howie et al 1993). However, other studies have shown that steroid-responsiveness, rather than histology, predicts good prognosis (Chun et al 2004).

Overall, in those patients who do not receive steroid treatment or do not respond, the rates of progression to ESKD appear to be similar. Despite the lack of RCTs of corticosteroids in FSGS, it seems clear that following a prolonged course of corticosteroids some patients achieve and sustain a remission of proteinuria, that at the very least, has useful prognostic utility, whether or not it contributes to improved renal functional outcomes.

What does should be used?

Most clinical studies have used prednisone doses of between 0.5 and 2 mg/kg/day to produce clinical remission. There is some evidence that doses of greater than 60 mg/day are more likely to induce remission than lower doses. In addition, alternate-day therapy (e.g. doses greater than or equal to 120 mg every second day) may be equally efficacious in FSGS and minimize toxicity. (Level III evidence)

What is the optimal duration of treatment?

Prolonged therapy (of at least 6 months) appears to be important both to sustain remission as well as to induce it. (Level III evidence)

How to define steroid-responsiveness?

Most steroid-responsive patients show some reduction in protein excretion within the first few months of therapy. The median time to clinical remission, when it occurs, is usually 3 to 4 months and most within 6 months of starting steroid therapy. It is therefore prudent that treatment should continue for at least 6 months before declaring the patient steroid-resistant. Although some patients will have remissions after this time, others have suggested that a lack of any decline in protein excretion at 8 weeks in children and 12 weeks in adults is generally indicative of steroid resistance. (Level IV evidence, anecdotal).

Background

FSGS is one of the most common primary glomerular diseases that result in renal impairment and ESKD. Patients with nephrotic-range proteinuria appear to be at the greatest risk of progressing to ESKD over the course of 3–6 years. Early treatment of patients with FSGS and nephrotic syndrome may alter the progression of renal disease in some patients. In particular, patients in whom a complete remission of proteinuria can be induced, may improve or stabilize their renal function. There is also some evidence that treatments that reduce proteinuria (partial remission) may also slow disease progression (Trojanov et al 2005). The objective of this guideline is to evaluate the available clinical evidence pertaining to the impact of steroid therapy on renal functional decline in patients with idiopathic FSGS.

Search strategy

Databases searched: MeSH terms and text words for focal segmental glomerulosclerosis were combined with MeSH terms and text words for steroid therapy. This search was carried out in Medline (1966 to September Week 2, 2004). The Cochrane Renal Group Trials Register was also searched for trials in focal segmental glomerulosclerosis not indexed in Medline.

Date of searches: 17 September 2004.

What is the evidence?

There have been no RCTs of corticosteroids in FSGS.

Summary of the evidence

While remission may be induced in patients receiving steroids, and steroid responsiveness correlates with improved outcomes, there have been no level I or II studies confirming the efficacy of this intervention in the preservation of renal function in individuals with primary FSGS.

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No prospective studies have specifically assessed the use of prednisone. Reports of case series support the use of prednisone at an initial dose of 60 mg/day for a minimum of four months; patients should not be considered prednisone resistant until a six-month trial of prednisone has been completed.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

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