Therapy-resistant focal and segmental glomerulosclerosis

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Abstract

The clinical course of a young female patient with focal segmental glomerulosclerosis (FSGS) who failed to respond to any of the recommended therapeutic protocols will represent the background of a discussion of currently available alternative treatments for FSGS. Traditionally, FSGS has been believed to have a poor prognosis, with a low response rate to treatment and a progressive course terminating with end-stage renal disease (ESRD). Some 40% of patients respond to prolonged corticosteroid treatment. Steroid resistance in adults should perhaps be assumed only after failure to respond to a 6-month course of daily steroid therapy. Regarding recent recommendations, the use of cytotoxic therapy (cyclophosphamide, chlorambucil or azathioprine) may be considered as second-line therapy (evidence D). Treatment with cyclosporin A at doses of 4–6mg/kg/day has been successful in reducing proteinuria. There is little information available on the effects of such treatment on the progression of FSGS. Even fewer data are available on the success rate of the use of tacrolimus in resistant forms of FSGS in adults. Mycophenolate mofetil has been used with impressive success in a few high-risk patients who failed on previous therapeutic regimens. There is preliminary evidence in an uncontrolled series of patients with resistant primary FSGS that the addition of plasmapheresis may provide effective long-term benefits in some patients. The accurate assessment of the role of plasmapheresis and possibly immunoadsorption in the management of patients with FSGS requires further evaluation. Non-immunosuppressive therapy (i.e. angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, lipid-lowering drugs, non-steroidal anti-inflammatory drugs) should be applied to almost all patients with primary FSGS.

Keywords: alkylating agents; calcineurin inhibitors; corticosteroids; nephrotic syndrome; plasmapheresis; primary focal and segmental glomerulosclerosis

Case presentation

An 18-year-old female who previously had been in excellent health presented with leg swelling and increasing body weight, developing over 3 weeks. She had no history of infection and other renal or systemic diseases. In her family history, there were no data regarding renal disease or hypertension. Physical examination revealed normal blood pressure, clear lungs, normal cardiac examination, no hepatosplenomegaly or signs of ascites, and 3+ pitting oedema in the legs. A full-blown nephrotic syndrome was confirmed by laboratory results. Serum urea, creatinine and creatinine clearance were normal. A first kidney biopsy revealed minimal change glomerulonephritis (McGN), and treatment with methylprednisolone (0.8mg/kg) was started. She was treated with a full dose for 20 weeks, after which the dose was slowly tapered. The interesting event of the initial course was almost a complete disappearance of proteinuria after 10 days of steroid treatment, with the reappearance of a nephrotic range proteinuria over the following 3 weeks. A second biopsy was performed after 6 months of treatment. A very good biopsy specimen (48 glomeruli, including juxtamedullary glomeruli) was obtained, but there were no abnormal glomerular changes and the first diagnosis of McGN was confirmed. Cyclophosphamide was introduced (2mg/kg/day) together with methylprednisolone (0.8mg/kg) and continued for 12 weeks. There was no effect on proteinuria; she remained hypoalbuminaemic and needed continuously high doses of furosemide (12mg per day) to be kept free of oedema. Cyclosporin A (CsA; 5mg/kg/day in two divided doses at 12h intervals) was started. The dose was adjusted to achieve 12h trough levels in the range 80–120ng/ml.

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A slight increase in serum creatinine, and the appearance of mild normocytic anaemia and hirsutism were noticed after 3 months of treatment. After 4 months of CsA treatment, all specific therapy was stopped due to inefficacy, steroid side effects (tendency to depression, signs of steroid myopathy and incipient cataract of both eyes), and a good clinical remission (no oedema) with supportive treatment. A low protein diet (0.5–0.6 g of protein/kg of body weight) together with an angiotensin-converting enzyme (ACE) inhibitor was continued for 6 months. We did not notice any decrease in proteinuria, and serum albumin (<25 g/l) and cholesterol (>9 mmol/l) concentrations were unchanged. In spite of her very good compliance from the beginning, the patient became weary of the unsuccessful treatment and abated in following our recommendations. The clinical picture of a nephrotic syndrome reappeared. A third biopsy was performed after 14 months. The light microscopy evaluation revealed a classical picture of focal and segmental glomerulosclerosis (FSGS). Methylprednisolone (0.4 mg/kg of body weight in alternate dose) was reintroduced, and tacrolimus at a total daily dose of 0.15 mg/kg in two doses at 12 h intervals was added 4 weeks later. The dose was then adjusted to achieve 12 h whole blood levels between 5 and 10 ng/ml. She had no serious side effects during this period except occasional nausea and morning vomiting. A slight increase in serum creatinine was noticed again. Tacrolimus was stopped after 13 months with a satisfactory clinical remission but with no effect on proteinuria, serum albumin or cholesterol concentrations. Non-specific treatment with a hypoproteinaemic diet, use of ACE inhibition (enalapril, 5 mg), small doses of diuretic (furosemide, 40 mg) and a lipid-lowering drug (simvastatin, 20 mg) was continued. Twenty-six months after the beginning of the disease, we decided to start membranous plasmapheresis. Methylprednisolone was reintroduced in a reduced dose (0.4 mg/kg of body weight). Twenty-four plasma exchanges in 16 weeks were performed. An increase in serum albumin from 18 to 31 g/l was observed, but no decline in proteinuria was found at this time (6.8 g/day at the start, 6.2 g/day at 3 weeks of plasmapheresis). There was a resolution of oedema and a decrease in her body weight to her pre-illness values. A relapse of a full-blown nephrotic syndrome appeared after 16 weeks, 1 week after the last plasmapheresis. The symptomatic treatment with diuretics was successful. Six weeks after the last plasmapheresis, a rescue therapy with mycophenolate mofetil (MMF) in a dose of 500 mg/8 h during meals was introduced. The patient was treated for 8 weeks and stopped after that due to serious gastrointestinal side effects (nausea, vomiting and diarrhoea). Thirty-five months after the diagnosis, the patient still has nephrotic range proteinuria (5.06 g/day), is hypoalbu- minaemic (23 g/l), with high cholesterol (11.2 mmol/l), with early renal insufficiency (creatinine 103 μmol/l) and a creatinine clearance of 40 ml/min.

**Introduction**

Primary FSGS is a clinicopathological entity that may affect both children and adults, and is characterized by proteinuria, most often severe, with sclerotic changes in some, but not all glomeruli, with sclerosis affecting only a portion and not the entire glomerular tuft. The incidence of FSGS has increased over the past 20 years for reasons unknown at this time. It accounts for 7–20% of glomerular lesions in both children and adults who present with proteinuria [1]. The cause of primary FSGS is by definition unknown. It is thought in some cases to result from an undefined circulating factor(s), possibly a cytokine or lymphokine, leading to epithelial cell injury resulting in abnormal glomerular permeability and possibly sclerosis in the final stage of this process [2].

Traditionally, FSGS has been believed to have a poor prognosis, with a <20% response rate to treatment and a progressive course terminating in end-stage renal disease (ESRD). However, some patients may show, for a long time, or sometimes indefinitely, a non-nephrotic range proteinuria and stable kidney function. Spontaneous remissions are rare, occurring in <5% of patients. Patients who succeeded in achieving a complete or partial remission with a decline in proteinuria have a better renal survival compared with those where therapy failed [3].

**Initial treatment and response**

Although FSGS was considered for a long time to be a steroid-resistant disease, several studies recently have shown a better responsiveness to more prolonged courses of corticosteroids [3,4]. Corticosteroids, prednisone or methylprednisolone, used for at least 3 months before tapering, became the mainstay of treatment of FSGS in adults. In the most recent review [5], the analysis of some important studies conducted since 1990 has shown a response rate to steroid treatment with complete remission in excess of 30%, with most being >40%. The most obvious difference causing a divergent response was the duration of therapy. A poor response was observed in those treated for <2 months compared with those treated for 5–9 months on average, with higher remission rate [3–6]. Persistent nephrotic syndrome and renal insufficiency at presentation may be associated with poorer prognosis. The severity of interstitial fibrosis can be the only predictor of response to therapy [6].

In summary, prolonged treatment with corticosteroids at a dose of 0.5–2.0 mg/kg of body weight given daily or on alternate days (prednisone) makes remission of nephrotic syndrome possible and can also help in preserving kidney function over time (treatment should continue for a total duration of 6 months before resistance to corticosteroid treatment can be accepted). However, one should be aware that
Other treatment possibilities

The benefit of adding immunosuppressive drugs such as cyclophosphamide, chlorambucil or azathioprine to corticosteroids is less clear. Most of the available studies are retrospective and, short term. These agents usually have been used as a second-line treatment either in frequent relapers or in patients resistant to steroid therapy. Analysis of a few recent retrospective studies showed that addition of cytotoxic agent to steroid-sensitive patients enabled complete remission in 50% of patients and partial remission in another 25% of cases. The response was lower in steroid-resistant patients (10% of patients given a cytotoxic agent entered complete and another 10% a partial remission) [8].

The first reports of treatment of idiopathic nephrotic syndrome with CsA were published in 1986. After 15 years of experience, it is clear that this drug is highly successful in steroid-responsive patients with subsequent relapse. A response was usually seen within the first month of treatment. The maximum cumulative rate of complete remission was achieved at 6 months, indicating that more prolonged therapy with CsA may only increase the risk of nephrotoxicity without hope of new remissions [8]. The dark side of a rather successful story is the fact that some 40 to >75% of treated patients relapse within 2 months of discontinuation or tapering of this agent [5,8,9]. In a recent paper on a randomized trial of CsA in patients with steroid-resistant FSGS (CsA + low-dose prednisone vs placebo + low-dose prednisone), Cattran et al. reported that 70% of 49 patients had complete or partial remission (only 4% in the placebo group) by 26 weeks; relapse occurred in 40% by 52 weeks and 60% by week 78 [9]. CsA treatment may be regarded as a good alternative to corticosteroids in FSGS patients, with a major concern relating to its nephrotoxicity and more rapid progression of renal disease. Appropriate adjustment of the CsA doses with regular monitoring of blood pressure and serum creatinine may reduce this risk.

Some experience in the treatment of steroid-resistant FSGS in children has been reported with tacrolimus, another calcineurin inhibitor. The experience with the use of this agent for the same indication in adults is limited. In a recent uncontrolled study, 25 patients with steroid-resistant FSGS, who were also CsA responsive or resistant, were treated with tacrolimus (0.15 mg/kg in two divided doses) and prednisone (1 mg/kg/day for 8 weeks, then tapered). Complete remission was achieved in 40% and partial remission in another 8% of patients (median time to remission was 120 days). The positive response to tacrolimus was associated with a previous response to CsA (remission rate for those responsive to CsA was 75% vs 15.3% in non-responders, \( P = 0.036 \)). Relapse occurred in 76% of patients after stopping therapy with tacrolimus [10].

Plasmapheresis and immunoadsorption as a rescue therapy have also been tried in patients with steroid-resistant FSGS. The rational for such treatment relied on the finding of as yet unidentified plasma factors in some patients with recurrent FSGS after kidney transplantation. Only a few trials have been done with such treatment in patients with FSGS on native kidneys. In a recent preliminary report, Mitwalli presented his experience of adding plasmapheresis to corticosteroids and alkylating agents in 11 patients with steroid-resistant primary FSGS. Each patient underwent on average 17 sessions. One month after the last plasmapheresis, eight patients (72%) were in clinical remission, with reduction of proteinuria below nephrotic range, and had stable renal function [11]. Hass et al. [12], using immunoadsorption in five patients with FSGS, found a reduction of proteinuria by >50% in four patients, with an additional clinical response in two patients with positive ‘permeability factor’. Since there are no data on the long-term effects of such an approach, plasmapheresis or immunoadsorption should be used only as a rescue therapy in high-risk patients with FSGS.

MMF, a newer immunosuppressive drug, has also been used sporadically in the treatment of steroid-resistant FSGS. Recently, Briggs et al. reported mixed results with the use of MMF in seven patients with FSGS [13]. The same group reported the newest experience with 18 patients (12 patients concomitantly received corticosteroids) suffering from FSGS. Complete or partial remission was observed in 12/18 patients. They concluded that besides short-term efficacy inducing remission, MMF had major steroid-sparing effects and could even be effective as monotherapy. Given the lack of nephrotoxicity and adverse haemodynamic and metabolic effects, they found MMF to be a suitable alternative to the calcineurin inhibitors as adjuvant treatment for many patients, especially those with progressive renal insufficiency [14].

Non-specific therapy

Jointly with specific immunosuppressive treatment of FSGS, many if not all patients will benefit from adjunctive, non-specific therapy. Control of blood pressure with the use of ACE inhibitors and angiotensin II receptor blockers reduces proteinuria up to 50% in patients with different primary glomerulonephritides, including FSGS. However, the use of ACE inhibitors alone has rarely led to...
remission of nephrotic syndrome in patients with primary FSGS [15]. The role of lipid-lowering drugs, non-steroidal and a hypoproteinaemic diet in this setting is less clear.

In conclusion, in spite of unconvincing evidence, there currently is more or less a consensus that prolonged corticosteroid therapy (for at least 6 months) should be offered to nephrotic patients with FSGS. Some 40–60% of patients with primary FSGS are resistant to steroids, and alternative immunosuppression therapy may be of value. As with all novel treatment strategies, however, the proper role for CsA, tacrolimus, MMF, cytotoxic drugs and plasmapheresis or immunoadsorption in the management of glomerular diseases can only be determined from prospective, well-designed clinical trials in appropriately stratified, large patient cohorts. Non-specific therapy (i.e. ACE inhibitors, angiotensin II receptor blockers, lipid-lowering drugs, non-steroidal anti-inflammatory drugs in some cases) should be applied to almost all patients with primary FSGS.

References