Other Immunosuppressive Agents for Focal Segmental Glomerulosclerosis

By Claudio Ponticelli and Patrizia Passerini

A prolonged course with corticosteroids represents the first therapeutic approach for nephrotic patients with focal segmental glomerulosclerosis (FSGS). In patients with contraindications to steroids or in those who do not respond to steroids or cyclosporine, cytotoxic agents, mycophenolate mofetil (MMF), plasmapheresis, and low-density lipoprotein (LDL) apheresis have been tried as alternative treatments. A short-term treatment with cytotoxic agents often is ineffective in steroid-resistant patients However, an aggressive and prolonged treatment with cytotoxic agents combined with corticosteroids proved to be effective in more than half of steroid-resistant children. In adults, the response to cytotoxic agents was good in steroid-responsive patients, but was poor in steroid-resistant patients. Better results were observed when cytotoxic therapy was prolonged for several months. The problem with these drugs is that long-term immunosuppression may be complicated by severe side effects including a major risk for cancer. Uncontrolled studies reported that MMF can induce some reduction of proteinuria , but complete remission of proteinuria was rare and no data on long-term follow-up evaluation with this drug are available. Good results have been reported with plasmapheresis, immunoadsorption, and lipopheresis. However, all the reports were uncontrolled, small sized, and with short-term follow-up evaluation. In conclusion, there are several therapeutic options for patients who respond to steroids and have further relapses of nephrotic syndrome, but how to treat steroid-resistant patients is still a matter of debate. Nevertheless, a 6-month trial with cytotoxic agents or MMF can be offered to steroid-resistant patients to identify the few patients who respond to these agents. The preliminary results with plasmapheresis or lipopheresis are promising but further studies are needed to assess the role of these treatments.

FOCAL AND SEGMENTAL glomerulosclerosis (FSGS) is a frequent cause of nephrotic syndrome both in children and in adults. FSGS can be secondary to a number of other diseases or disorders, but in many cases no etiologic factors can be identified and the disease is called idiopathic or primary.

Before planning a therapeutic strategy the nephrologist should therefore establish whether the disease is primary or secondary. The history of the patient and/or the pre-existence of diseases that can be associated with FSGS may suggest that the patients has secondary FSGS (Table 1). Other diagnostic clues are the rarity of the nephrotic syndrome and the slower progression in the secondary forms. At biopsy examination, the secondary FSGS may show a marked glomerulomegaly, periglomerular fibrosis (especially in cases of reflux nephropathy), thickening of glomerular basement membrane (particularly in patients with diabetes mellitus), and less foot process effacement than in the idiopathic form.

The treatment of secondary FSGS depends on the etiology, but in most cases it does not differ from the guidelines recommended for preventing or slowing the progression of renal disease.[1]

The treatment of idiopathic FSGS is still far from being established. Nonnephrotic patients, including the few nephrotic patients who have reduction in urine protein levels to less than 2 g/d on angiotensin antagonist therapy usually do not progress to renal failure,[2-5] are not exposed to the possible complications of the nephrotic syndrome, and generally are asymptomatic. Therefore, specific treatment is not recommended for these patients.

Unfortunately, however, most patients with FSGS either present with or develop later a nephrotic syndrome. Only exceptionally a spontaneous remission of proteinuria may occur in nephrotic patients with FSGS. In those patients who remain nephrotic, approximately two-thirds inexorably progress to end-stage renal failure within 10 to 15 years from clinical onset.[6] A number of studies have shown that prolonged corticosteroid treatment may favor remission of proteinuria and protect from renal dysfunction both in children[6-8] and in adults.[9-13] However, some patients do not respond to corticosteroids, others do not tolerate a

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Table 1. Causes of Secondary FSGS

Reflux nephropathy
Oligomeganephronia
Unilateral agenesia
Renal nephron number reduction beyond uninephrectomy
Scarring (necrotizing lesions)
Renal infarction
Diabetes mellitus
Morbid obesity
Congenital heart disease
Hereditary nephritis
Nail-Patella syndrome
Sickle-cell nephropathy
Pamidronate
Parvovirus B19
Acquired immune deficiency syndrome

prolonged treatment, and many responders become either frequent relapsers or steroid dependent. As a consequence, alternative drugs and combination of drugs have been used for the treatment of FSGS.

In this article we review the results obtained with immunosuppressive strategies and/or plasma exchange in children and in adults. We will not deal with the use of calcineurin inhibitors, which is discussed in another article in this issue.

CYTOTOXIC AGENTS

Children

Cyclophosphamide and chlorambucil (less frequently) have been the cytotoxic agents most widely used in treatment of FSGS. The results in steroid-responsive children usually are good. Cyclophosphamide at a dose of 2 mg/kg/d or chlorambucil 0.15 to 0.2 mg/kg/d, for 8 to 12 weeks, may induce complete or partial remission in about two thirds of patients.[7,8,14]

Less favorable are the results in children with steroid-resistant FSGS. A review of retrospective studies showed that 51 of 190 (26%) children given cytotoxic drugs were in complete remission after follow-up periods of different lengths.[15] Such a large variation partly may be accounted for by the different definition of steroid resistance and by the different doses and duration of cytotoxic therapy. There is only one controlled trial with the use of cyclophosphamide in children with FSGS.[16] In that trial 63 children with steroid-resistant nephrotic syndrome (no response after prednisone 60 mg/m^2 for at least 28 days) were allocated randomly either to prednisone (40 mg/m^2 every other day for 1 year) or to the same regimen of prednisone plus cyclophosphamide (2.5 mg/kg/d for 3 mo). After a follow-up period ranging between 1 and 7 years, the percentage of patients in complete remission was 27% in each group.

Prospective studies evaluated the role of intravenous pulse cyclophosphamide infusions. Rennert et al[17] administered intravenous cyclophosphamide (500 mg/m^2 every month for 6 mo) plus high-dose prednisone for 2 months, followed by alternate-day prednisone for 10 months, to 10 children. In 5 steroid-resistant patients, 2 complete remissions and 1 partial remission were obtained. In the other 5 patients who were initially frequent relapsers and then became steroid resistant a sustained remission was achieved. No major side effects were observed. In an Indian study,[18] 20 children with steroid-resistant FSGS were given intravenous cyclophosphamide (500-750 mg/m^2 every mo) plus oral prednisolone given daily (60 mg/m^2) for 4 weeks, and then every other day for 12 weeks. After a mean follow-up period of 21 months since completion of therapy, 13 of 20 children (65%) were in complete remission. However, the definition of steroid resistance was unclear because 10 children were infrequent relapsers, 2 were frequent relapsers, and 1 was steroid dependent.

An aggressive treatment with repeated intravenous pulses of high-dose methylprednisolone plus alternate-day prednisone over 18 months plus cyclophosphamide or chlorambucil for 8 to 12 weeks was proposed by Mendoza et al[19] for steroid-resistant children. Five groups reported the results of this regimen, with little modifications.[20-24] Taking together the data of these studies, of 121 steroid-resistant children treated with the Mendoza et al's[19] regimen, 45 (37%) entered complete remission of proteinuria and 15 (12%) attained a reduction of proteinuria to a nonnephrotic range. Remission tended to remain stable. The regimen was well tolerated but a few patients developed infection, transient hypertension, and growth retardation.

Adults

Alkylating agents gave variable results also in adults. An analysis of retrospective studies showed that in steroid-responsive patients, cytotoxic drugs could obtain complete remission in 50% of cases and partial remission in another 25% of patients. The response was much lower in steroid-resistant

patients. Only 10% of patients entered complete remission and another 10% achieved partial remission.[14] In most of the analyzed studies, cytotoxic agents were administered for 2 to 3 months. It is possible that longer treatments may give better results. Banfi et al[10] treated 32 nephrotic adults either with chlorambucil alternated with high-dose steroids every other month for 6 months or with cyclophosphamide plus small doses of prednisone for a mean period of 25 months. A complete remission of proteinuria was observed in 17 patients. After a mean follow-up period of 75 months, 15 of the 32 patients (47%) were in complete remission, another patient had asymptomatic proteinuria, 2 were still nephrotic, 8 were on dialysis, 5 had renal insufficiency, and one died. Of interest, relapse of nephrotic syndrome occurred only in 3 of 17 patients, or 18%, a rate clearly inferior to the 50% reported in patients who responded to steroids who had a relapse of nephrotic syndrome.[10]

When given as a first-line treatment, cytotoxic agents administered in median for 75 weeks obtained complete remission in 30% of patients and partial remission in another 11%. Relapse of the nephrotic syndrome occurred in only 27% of the responders.[13]

In summary, there is not evidence that an 8- to 12-week treatment with cytotoxic agents is superior to corticosteroids in inducing remission either in children or in adults. However, when compared with steroids, these agents may prolong the duration of remission in responders. Long-term administration of oral cytotoxic agents may obtain complete or partial remission in a few steroid-resistant patients. It should be reminded, however, that a cumulative dose higher than 300 mg/kg for cyclophosphamide[25] or 10 mg/kg for chlorambucil[26] may expose the patient to gonadal toxicity. Moreover, prolonged administration of alkylating agents may be associated with an increased risk for malignancy. Both cyclophosphamide and chlorambucil have been included among the agents with a potential carcinogenic effect. Although there is not any systemic study on the dose-related oncogenic agents it would be prudent not to use these drugs for more than 6 months. More prolonged regimens as well as aggressive and prolonged treatments based on the combination of repeated intravenous high-dose steroid pulses, oral prednisone, and oral cytotoxic drugs may be considered for patients with severe nephrotic syndrome or progressive disease.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is an inhibitor of purine synthesis, which largely is being used in transplant patients. Its relatively mild safety profile makes MMF an attractive possibility in glomerular diseases, including FSGS.

Children

Bartosh[27] used MMF at a mean dose of 892 $\pm$ 197 mg/m^2/d in 2 children with FSGS partially responsive to corticosteroids. One patient achieved a complete remission on MMF and the second patient maintained a partial response. Although both children had already reached a response as a result of the previous corticosteroid treatment, the substitution of corticosteroids with MMF obtained an improvement in their clinical status. Montane et al[28] treated 7 steroid-resistant children/young adults with low-dose MMF (300-500 mg/m^2/d) for 12 to 36 months. Before starting MMF, 5 of 7 patients were placed in partial remission with weekly intravenous high-dose corticosteroid therapy (15 mg/kg/wk for 6-8 wk). During MMF treatment, all patients showed a response with disappearance of proteinuria in 2 cases and a 50% reduction of proteinuria in the other 5 patients.

Adults

Al-Lehbi et al[29] administered MMF to 10 patients with FSGS who were resistant to steroids and were either cyclosporine dependent or resistant. Patients received MMF 1.5-2 g/d plus prednisone for a total of 6 months. There was only a mild decrease of proteinuria from 12.6 to 10.8 g/d. All patients were still nephrotic at the end of treatment. Matalon et al[30] administered MMF to 11 adults with FSGS and nephrotic syndrome, at a mean dose of 1,275 mg/d, for a mean period of 28 weeks. The treatment induced a reduction in proteinuria from 6.8 to 5.7 g/d, which was statistically significant but of little clinical relevance. In no patients did proteinuria decrease to a level below 2.5 g/d.

Choi et al[31] reported the outcome for 18 patients with FSGS dependent or resistant to corticosteroids or cyclosporine, or with progressive renal insufficiency. Twelve patients had renal insufficiency and 9 had nephrotic syndrome. These pa-

tients received MMF at initial doses of 1 to 1.5 g/d for at least 3 months, plus variable doses of steroids in 12 of them. The 24-hour urine protein to creatinine ratio significantly decreased from 2.7 to 0.8 (median 48%) at the end of the MMF treatment. Among the 9 nephrotic patients 1 had a complete remission and 4 had a partial remission. Median serum creatinine level increased from 1.9 to 2.2 mg/dL. In the 12 patients receiving concomitant steroid therapy, prednisone could be stopped completely without relapse in 8 cases. One patient relapsed and steroid treatment was resumed, and 3 others continued on low-dose steroid treatment. MMF generally was well tolerated.

In summary, it is difficult to draw any conclusion from these preliminary experiences. There is the impression that patients may obtain a short-term benefit from MMF therapy, which may reduce proteinuria and may decrease the cumulative dosage of steroids. However, it must be pointed out that all the available studies were not controlled and were based on short-term treatment. Nothing is known about the possibility that MMF may alter the progression of FSGS, nor do we have information about the optimal doses and the length of treatment with MMF. Well-designed, prospective, randomized trials are needed to assess the role of this agent in FSGS.

PLASMAPHERESIS AND IMMUNOADSORPTION

A number of experimental and clinical studies[32-34] have suggested a pathogenetic role for a circulating plasma factor in FSGS. This factor appears to be a 30- to 50-kd plasma protein bound to immunoglobulin G, which increases the glomerular permeability to albumin. Because this factor may be removed by plasma exchange or by immunoadsorption with protein A, these techniques have been used in the management of drug-resistant FSGS. Complete or partial remission of the nephrotic syndrome has been obtained in several patients with posttransplant recurrence of FSGS. The response has been reported to be better in children than in adults.[30] Recently, this approach also has been attempted in patients with FSGS on the native kidneys.

Children

Vecsei et al[35] achieved remission of nephrotic syndrome after 5 sessions of plasmapheresis in an 8-year-old boy with FSGS resistant to steroids, cyclosporine, and MMF.

Adults

Ginsburg and Dau[36] obtained a dramatic decrease in proteinuria, from 8.8 to 2.0 g/24 hr, and in serum creatinine level, from 2.9 to 1.0 mg/dL, in an adult patient with resistant FSGS and severe nephrotic syndrome, treated for 18 months with weekly plasmapheresis combined with moderate doses of prednisone and azathioprine. Mitwalli et al[37] reported the outcome of 11 adult patients with FSGS resistant to prolonged immunosuppression who were treated with plasmapheresis in a mean of 17 sessions over a period of 15 to 25 weeks, in combination with oral prednisolone 60 to 80 mg daily, and intravenous cyclophosphamide, 5 to 10 mg/kg monthly, for 6 months. Eight patients responded to plasmapheresis with a stabilization of renal function, associated with a long-lasting complete remission in 6 patients (54.5%) and a partial remission in 2 other patients (18.2%). The remaining 3 patients who did not respond to plasmapheresis developed progressive renal insufficiency and 2 of them reached end-stage renal failure. No severe side effects were noted in any of the studied patients. Feld et al[38] treated 8 steroid-resistant adults with 6 plasmapheresis sessions over 2 weeks. Proteinuria decreased in 2 patients, although only transiently in 1 of the 2 patients. Both the responders had stable renal function at the last follow-up evaluation. In contrast, 4 of the 6 nonresponders had a progressive decline of renal function or were receiving dialysis treatment. No relationship between the circulating permeability factor and the development of remission was observed. Haas et al[39] assessed the effects of immunoadsorption on proteinuria and the predictive value of the permeability factor in serum measured with glomerular volume variation in 5 adults with FSGS. Immunoadsorption reduced proteinuria by more than 50% in 2 of 5 patients. In one responder the glomerular volume variation test, which was positive before treatment, became negative after the first immunoadsorption cycle. The other 4 patients had negative glomerular volume variation test results both before and after immunoadsorption.

In summary, an analysis of the available studies showed that plasmapheresis or immunoadsorption could obtain a partial or complete remission of nephrotic syndrome in 14 of 26 patients (54%)

Table 2. Extracorporeal Plasma Treatment of FSGS Occurring in Native Kidneys

Study	Patients	Remission	Treatment
Vecsei, 2001[35]	1 child	1	Plasmapheresis
Ginsburg, 1997[36]	1 adult	1	Plasmapheresis
Mitwalli, 1998[37]	11 adults	8	Plasmapheresis
Feld, 1998[38]	8 adults	2	Plasmapheresis
Haas, 1998[39]	5 adults	2	Immunoadsorption
Total	26	14 (54%)	

with severe FSGS (Table 2). However, the lack of relationship between the removal of the circulating permeability factor and the response to treatment observed in some patients suggests that some other local or systemic factors may play an important role in determining proteinuria in FSGS. Moreover, there is not agreement among the experts on the actual nature of the plasma factor. It even could be possible to speculate that not only the presence of a permeability factor but also the absence of some protective factors could concur to the pathogenesis of FSGS.[40]

Clearly, further studies with long-term follow-up evaluation and a larger number of patients are needed to confirm these preliminary results. Well-designed, prospective, randomized trials could eventually assess the actual role of plasmapheresis and/or immunoabsorption with protein A in FSGS, could better clarify the nature of the permeability factor(s) in this disease, and could help in identifying those patients who may benefit from these techniques.

LOW-DENSITY LIPOPROTEIN APHERESIS

Treatment with various lipid-lowering regimens has been claimed to be able not only to improve hyperlipidemia, but also to reduce proteinuria in nephrotic syndrome,[41,42] although a true remission rarely occurs. Therefore, a more aggressive lipid-lowering strategy, using low-density lipoprotein (LDL) apheresis has been attempted in patients with steroid-resistant FSGS. Some anecdotal reports pointed out a good effect of LDL apheresis on proteinuria.[43,44] In a Japanese study,[45] 14 patients with steroid-resistant nephrotic syndrome owing to FSGS were treated with a total of 6 sessions of LDL apheresis (2 times a wk for 3 wk) plus corticosteroids. Urinary protein excretion decreased from 7.2 ± 3.5 to 2.5 ± 2 g/d and the glomerular filtration rate increased from 54.4 ± 27.4 to 70 ± 30.2 mL/min. The improvement persisted for more than 6 months. Renal biopsy examination was repeated in 6 patients in whom proteinuria decreased below 3.5 g/d at 3 months after treatment. Although there was no change on light microscopy, electron microscopy showed that the previous severe fusion of the foot processes of podocytes was decreased. Muso et al[46] treated 17 adult patients with FSGS who did not respond to 1 month of full-dose steroid treatment with LDL apheresis twice a week for 3 weeks, followed by weekly LDL apheresis for 6 weeks, plus full-dose corticosteroids. Complete remission was obtained in 8 patients and incomplete remission was obtained in 4. The average duration needed for a decrease of proteinuria to less than 3.5 g/d was 14.7 ± 19.6 days.

In summary, lipopheresis seems to be a novel and promising approach for treating nephrotic syndrome in steroid-resistant patients with FSGS. Once again, however, the available studies are based on small series with short-term follow-up periods, leaving many questions unsolved such as indications, length of treatment, effect on renal function, and so forth.

CONCLUSIONS

How to treat nephrotic patients with idiopathic FSGS is still controversial. There is agreement that these patients should receive a symptomatic treatment aimed to maintain blood pressure below 125/75 for patients with proteinuria greater than 1 g/d, to correct hyperlipidemia, and to reduce proteinuria with angiotensin-converting enzyme inhibitors and/or angiotensin-2 receptor blockers. However, although useful, these measures only rarely can obtain a reversal of the nephrotic syndrome.

Corticosteroids may obtain remission of the nephrotic syndrome in 50% to 60% of patients but

treatment should last several months and may be associated with side effects, particularly in frequent relapsers. Calcineurin inhibitors may be helpful in steroid-dependent patients and may induce remission in few steroid-resistant patients. However, proteinuria usually reappears when these agents are stopped.

The role of alternative approaches is undefined. The use of cyclophosphamide and chlorambucil is still under discussion. The impression is that those agents may be effective in some patients only when administered for a long period of time. However, such an approach may expose the patient to the risk for oncogenic and gonadal toxicity. A possible compromise could consist of alternating corticosteroids with an alkylating agent every other month for 6 months, as in membranous nephropathy,[47] but only few patients with FSGS received such a treatment so that it is impossible to evaluate the effectiveness of this approach. The results with MMF are scanty and preliminary. We need to know whether a long-term treatment with MMF may produce a consistent reduction of proteinuria and a protection of renal function, though the available articles report information only on few patients with short-term treatment. The results with plasmapheresis and LDL apheresis in patients with nephrotic syndrome resistant to other therapies are promising. Once again, however, the available data refer to few patients with short-term follow-up periods.

In conclusion, the treatment of idiopathic FSGS remains elusive. This is disappointing if one takes into account that this disease is a frequent cause of nephrotic syndrome and end-stage renal failure in children and in adults. New therapeutic trials are urgently needed in this orphan disease.

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