Treatment of idiopathic nephrosis by immunophillin modulation

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Abstract

Until 1985, glucocorticoids and cytotoxic drugs were the only treatments available for idiopathic nephrotic syndrome (nephrosis), that is, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Trials of cyclosporine (CsA) treatment of nephrosis, the rationale of which was based on pathophysiologic considerations, have shown that this immunophillin modulator is effective in inducing and maintaining remission in patients suffering from idiopathic nephrotic syndrome. It appears that the best results, in the order of 80% remission rate, are obtained in steroid-sensitive cases, essentially MCD, and that in steroid-resistant FSGS the drug obtains remission in no more than 20% of the cases. Addition of glucocorticoids increases the success rate to ~30% of cases. Renal toxicity is proportional to previous impairment of renal function, primary renal disease (FSGS vs MCD) dosage > 5.5 mg/kg/day and duration of treatment. The better bioavailability of the new formulation of CsA (Neoral), implies that the former dosage recommendations be reconsidered for distinctly lower figures. Repeat renal biopsy after 1 year of continuous CsA treatment is advisable, as stable serum creatinine levels may be falsely reassuring. CsA dependency is the rule during the first year of treatment. However, in some 25% of cases stable remission may be maintained after slow tapering off following 3–4 years of treatment. Other immunophilin modulators have been tried in the treatment of idiopathic nephrotic syndrome. Despite few preliminary reports indicating some success of tacrolimus the effects of this drug do not seem convincingly superior to CsA in terms of remission rate, toxicity and dependency. Rapamycin has not been tried in the treatment of nephrosis. Anecdotal cases of de novo FSGS induced by rapamycin in transplanted patients might indicate that this drug is in fact contraindicated in the treatment of nephrosis.

Keywords: adults; children; cyclosporine; focal segmental glomerulosclerosis; immunophillin modulation; idiopathic; nephrosis; nephrotic syndrome; minimal change disease; rapamycin; sirolimus; tacrolimus; treatment

Introduction

Until 1985, glucocorticoids and cytotoxic drugs were the only treatments available for idiopathic nephrotic syndrome (nephrosis), which is, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). Then, 2 years after cyclosporine A (CsA) had been introduced in organ transplantation, some investigators reasoned that the generally accepted pathophysiology of nephrosis was the consequence of T lymphocyte-driven secretion of a lymphokine that induced loss of negative charges in the glomerular polyanionic structures. We refer the reader to the relevant contributions in this issue [1–3]. The best-known mode of action of CsA was its inhibitory effect on interleukin-2 (IL-2) secretion. Therefore, it was not illogical that CsA would also impede secretion of a lymphokine responsible for nephrosis. In fact, the first abstracts and papers that appeared in 1985 and 1986 indicated that CsA was efficient in controlling the nephrotic syndrome of MCD, essentially in corticosteroid-dependent and multi-relapsing forms, that its efficacy in FSGS was less, essentially in corticosteroid-resistant cases, and that its short-term tolerance was acceptable. Since that time, a flurry of publications has appeared. They call for three comments. First, the impression left by the initial trials has been amply confirmed in that the efficacy of CsA was largely anticipated from the previous response of nephrosis to steroids. Secondly, the results of treatment trials in various parts of the world regarding efficacy and tolerance vary, however, from enthusiasm to discouragement. Thirdly, the issue of CsA treatment of nephrosis is marred by the low number of controlled trials. In the meantime, a few publications presented the results of the treatment of nephrosis with drugs that,
like CsA, operate through immunophillin modulation. Considering the title of this paper, it seems appropriate to make a rapid overview of the mode of action of three immunosuppressors that are or might be indicated for treating nephrosis: CsA, FK506 and rapamycin.

Cyclosporine A, tacrolimus, sirolimus and intracellular signal transduction pathways

A T cell-driven immune response develops in three phases. The first involves transcriptional activation of early genes such as the IL-2 receptor that elicits progression of T cells from the G₀ to the G₁ state. In the second phase, T cells transduce the signal triggered by specific cytokines that permit entry into the cell cycle, resulting in clonal expansion and effector functions in the third phase of the immune response. FK506 and CsA inhibit the first phase. Sirolimus interferes with the second phase of T cell activation [4]. So far, no drugs have been developed that would act on the third phase. Both sirolimus and tacrolimus bind to the same family of immunophillins, cytosolic FK binding proteins (FKBP). Thus, contrary to CsA, tacrolimus and sirolimus act as prodrugs that are activated only by formation of a drug–FKBP complex.

CsA and FK506

Despite distinct chemical structures, CsA and FK506 have almost indistinguishable cellular effects [5]. Both interfere with a cytosolic binding protein. Regarding CsA, the binding protein was dubbed cyclophilin, a potent inhibitor of rotamase activity. FKBP, the binding protein for FK506, is also highly basic and abundant in the cytosol. It has no sequence homology with cyclophilin, but similarly possesses rotamase activity that is inhibited by FK506, but not by CsA. The basic data suggested that rotamase inhibition explains the immunosuppressive action of CsA and FK506. In fact, rapamycin and its analogues, which inhibit the rotamase activity of FKBP are incapable of blocking TCR-induced IL-2 transcription. In addition, molecular variants of CsA that are poor inhibitors of the rotamase activity of cyclophilin retain a significant amount of immunosuppressive activity. Inhibition of signal transduction operates through complexes formed between immunosuppressants and immunophillins that interact with other cellular components. It was found that the FKBP–FK506 and the cyclophilin–CsA complexes bind to the same set of target proteins, calmodulin and calcineurin. FK506 or CsA cause inhibition of calcineurin through binding with immunophillins. In brief, the immunosuppressant activity of both FK506 and CsA is to inhibit calcineurin activity in T cells. This specifically impedes the TCR mediated transcription of the IL-2 gene.

The last step of the immunosuppressant action of FK506 and CsA requires the identification of the retaining signal to the nucleus to activate IL-2 transcription. The promoter region of the IL-2 gene has a binding site for NF-AT, a T cell-specific transcription factor. It is the nuclear translocation of cytoplasmic NF-AT (NF-ATc) that is inhibited by CsA and FK506. NF-ATc, the direct substrate of calcineurin, appears to be the last protein messenger of a signal transduction cascade relaying the signal from the TCR on the cell surface, through calcineurin in the cytoplasm, to the nucleus.

Over the past years, a host of cyclophilin and FKBP isoforms have been identified. Inhibition of the phosphatase activity of calcineurin is operated through a cyclophilin A–CsA complex. FK506 operates through binding to FKBP12. However, the calcineurin recognition surfaces of cyclosporin–cyclophilin and FK506–FKBP are remotely similar. Their binding to calcineurin is mutually exclusive, and how the two different complexes can bind to the same target is still an open question.

Both CsA and FK506 exert cellular effects other than that on TCR mediated signal transduction. Both have been tried in the treatment of nephrosis. Both are nephrotoxic. However, the molecular mechanisms of their nephrotoxicity remain largely unknown.

Rapamycin (sirolimus)

Contrary to CsA and tacrolimus, which inhibit the production of cytokines, sirolimus inhibits the response to these cytokines [6–8]. It has no effect on the expression of early phase T cell-activation genes for IL-2, IL3, IL4, GM-CSF and TNF. Once complexed with FKBP, sirolimus forms a complex, sirolimus–FKBP–FRAP that arrests the cell cycle at the G₁–S interface. This leads to blocking the synthesis of ribosomal and elongation factors required for protein synthesis, necessary for progression of T cells into S phase that is regulated by cyclin-dependent kinases. Sirolimus prevents the complex from becoming catalytically active due to the persistence of the cdk inhibitor p27kip1 that produces cell arrest in G₁. A major advantage of sirolimus is its lack of nephrotoxicity. Its most common side effect is hyperlipidaemia.
Cyclosporine A

Mode of action in nephrotic syndrome

It is essential to understand that the mode of action of CsA in nephrotic syndrome is 2-fold (for review see [9,10]).

The pharmacological effect of CsA, that most likely has nothing to do with immunosuppression, is a diminution of proteinuria, the mechanism of which is probably complex. CsA induces a vasoconstriction of the glomerular afferent arteriole, which in itself reduces the urinary protein output along with a rise in serum creatinine levels. Secondly, in addition to this purely haemodynamic effect, CsA interferes with the glomerular basement membrane permselectivity to proteins, as shown in numerous experimental protocols in the human [11] and in the experimental animal [12,13]. These anti-proteinuric effects of the drug explain why in forms of nephrotic syndrome that have no immunologic background, such as Alport's syndrome and diabetic glomerulosclerosis, CsA is effective in reducing proteinuria and raising serum albumin levels. Thus, the results of treatment trials in nephrosis must be cautiously interpreted in view of this non-specific anti-proteinuric effect that occasionally is labelled 'partial remission' but does not necessarily mean that the primary renal disease is following a favourable course. In some cases of FSGS, repeat biopsy showed that despite remission of proteinuria, the glomerular lesions worsened [14] and that despite reassuring stable serum creatinine levels, interstitial fibrosis increased [15].

Conversely, the mechanism by which CsA-induced immunodepression unpredictably leads to complete remission in a subset of patients with nephrosis is still unknown. The best-known mode of action of CsA is to hamper IL-2 secretion, but IL-2 is not the offending agent responsible for nephrosis. In 1988, Tejani et al. [16] observed higher IL-2 activity in supernatant from PHA-activated PBM of responders than in supernatant obtained from non-responders. As interesting as this finding may be, it provides no clue for explaining why some patients are CsA-responsive whereas others, with the same histological lesions, are totally unresponsive. The same remark was made by McCauley et al. [17] regarding response to FK506, which led them to hypothesize that such differences in the response to the same drug of the same subset of idiopathic nephrotic syndrome suggests different pathophysiological mechanisms.

Open trials

The first therapeutic trials of nephrosis with CsA date back to 1985 [18–21]. These trials were followed by innumerable publications, comprising original papers with a few cases, and many abstracts. Different methodology, dosage and definitions of complete and partial remission make it a difficult task to pool the data. However, some large series provide consistent data regarding the efficacy of CsA in adults and children with idiopathic nephrosis, regardless of renal histology (MCD or FSGS).

Sandoz Pharma [22] and Meyrier, Niaudet and Brodehl [23] analysed pooled data from seven open trials comprising a total of 341 patients with nephrosis. There were 213 adults and 128 children. 68.5% of the whole population was steroid-resistant and 31.5% steroid-dependent. Proteinuria significantly decreased and serum albumin significantly increased in the whole population. The overall rate of complete remission was 37%. Table 1 shows that the rate of complete remission was significantly higher in steroid-dependent (80%) than in steroid-resistant (19%) patients, and in MCD (60%) compared with FSGS (20%). In steroid-resistant cases the rate of complete or partial remission was significantly higher with CsA plus low-dose prednisone (48%) than with CsA alone (26%). Corticosteroid resistance was not only highly predictive of resistance to CsA but also of decline in renal function over the first year of treatment. This was the case for >35% of steroid-resistant cases, a majority of whom, had FSGS. In patients with steroid-resistant nephrosis, combining steroids with CsA, as shown in Table 2, increased the overall rate of complete and partial remission. However, the rate of complete remission and of partial remission were each not higher than 24%.

Table 1. Pooled data from seven open clinical studies as of 1992, comprising a total of 341 patients treated with CsA with the aim of inducing remission of idiopathic nephrosis (source [23])

<table>
<thead>
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<th></th>
<th>n</th>
<th>Complete remission</th>
<th>Partial remission</th>
<th>Failure</th>
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<tbody>
<tr>
<td>All</td>
<td>341</td>
<td>37%</td>
<td>15%</td>
<td>48%</td>
</tr>
<tr>
<td>Adults</td>
<td>213</td>
<td>38%</td>
<td>18%</td>
<td>44%</td>
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<tr>
<td>Children</td>
<td>128</td>
<td>36%</td>
<td>11%</td>
<td>53%</td>
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<tr>
<td>Histology</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>MCD</td>
<td>146</td>
<td>60%</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>FSGS</td>
<td>195</td>
<td>20%</td>
<td>19%</td>
<td>61%</td>
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<td>Steroid statusa</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Steroid dependent</td>
<td>104</td>
<td>80%</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Steroid resistant</td>
<td>226</td>
<td>19%</td>
<td>18%</td>
<td>63%</td>
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aUnknown in 11 patients.
Niaudet and Habib [24], in an editorial review on CsA in the treatment of idiopathic nephrosis, pooled the results of 16 studies on CsA treatment in steroid-sensitive/dependent and steroid-resistant idiopathic nephrosis. The results of their compilation are summarized in Table 3. They are in agreement with the foregoing data and show that complete remission is at best achieved in 20% of corticosteroid-resistant patients.

In order to evaluate chronic nephrotoxicity of CsA, Habib and Niaudet carried out a first post-treatment biopsy in 42 patients after 4–28 months of CsA, a second biopsy in 23 after 18–42 months of CsA and a third biopsy in eight after 30–63 months of CsA. Overall, this study [25] showed a steady increase in tubulointerstitial lesions and fibrosis despite falsely reassuring stable renal function.

Personal experience

A registry was initiated in 1986 to centralize the results of CsA treatment of idiopathic nephrotic syndrome. The patients originated from 59 nephrology units in France, Switzerland, Luxembourg and Germany. The first patient was included in January 1986 and the last in April 1996. The results in the first 112 patients are to be found in [10]. Total inclusions were 195. However, complete information was available in only 150. The longest duration of treatment at end point was 10 years. The following results concern 150 cases that were considered valid for assessing efficacy and tolerability, after eliminating wrong inclusions and grossly incomplete files (Table 4). At the beginning of treatment with CsA, 85 patients were diagnosed as MCD; 75 were fully nephrotic, seven were proteinuric only and three multirelaters were in remission. Duration of nephrotic syndrome had been 52.3 ± 70 months (range 2–310). Sixty-five patients were diagnosed as FSGS. All were nephrotic, and duration of nephrotic syndrome had been 47.5 ± 65 months (range 4–274). The results of CsA treatment, classified as complete remission, partial remission and failure, are given in Table 4, where these categories are also defined.

Minor side effects of CsA were common, but rarely if ever led to discontinuation of treatment. Conversely, hypertension requiring treatment was noted in 19% of patients, mainly those with FSGS. The most important point considered was renal tolerance, which depended on the type of primary renal disease, the pre-treatment level of renal function, the dosage administered and the quality of renal function monitoring applied in the course of treatment [14].

Regarding MCD, provided that CsA dosage was not >5.5 mg/kg/day, serum creatinine levels were 85.2 ± 26.9 μmol/l before treatment and 87.3 ± 24.8 μmol/l at end point. In contrast, in patients with FSGS, serum creatinine levels were 117.1 ± 48.3 μmol/l before treatment and rose to 130.6 ± 60.1 μmol/l at end point. In a

| Table 3. Pooled data from 16 publications as of 1992 on the results of CsA treatment of nephrosis in adults and children (summarized from [24]) |
|-----------------|-----------------|-----------------|
|                  | Corticosteroid-sensitive/dependent | Corticosteroid-resistant |
|                  | No. of patients | Complete remission | No. of patients | Complete remission |
| Children         | 129             | 109 (84.5%)       | 60              | 12 (20%)          |
| Adults           | 33              | 25 (76%)          | 49              | 6 (15%)           |

| Table 4. Response of idiopathic nephrotic syndrome to CsA treatment according to renal histology and to prior response to corticosteroid therapy in 150 adult patients (Société de Néphrologie Collaborative Study Registry) |
|------------------------|------------------------|
| Response according to histology | Response according to prior corticosteroid sensitivity* |
| MCD n = 82 | FSGS n = 68 | Sensitive n = 66 | Resistant n = 81 |
| CR | 60 (74%) | 14 (21%) | 48 (72%) | 24 (30%) |
| PR | 11 (13%) | 19 (28%) | 9 (14%) | 21 (26%) |
| F  | 11 (13%) | 35 (51%) | 9 (14%) | 36 (44%) |

CR, complete remission (reduction in proteinuria to <0.5 g/24 h and normalization of serum albumin level); PR, partial remission (proteinuria >0.5 but <3.5 g/24 h and serum albumin ≥3 g/dl); F, failure (no remission of nephrotic syndrome after 6 months of CsA treatment).

*Note: CsA was first-line treatment in three patients considered as having a contraindication to corticosteroid treatment (duodenal ulcer, psychosis, morbid obesity).
majority of cases, rising creatinine led to stopping treatment and later heralded progression to end stage renal failure.

Abnormal renal function, defined by serum creatinine > 200 μmol/l before starting CsA in patients with corticosteroid-resistant FSGS was highly predictive of a rapid progression to ESRD with CsA. The maximum acceptable dosage was 5.5 mg/kg/day, and the most severe lesions observed on repeat renal biopsy were in patients with FSGS whose serum creatinine was 132 ± 44.5 μmol/l before starting CsA and who had been treated with an average dosage of 6.26 ± 1.05 mg/kg/day.

The cumulative rate of complete remission (80% in steroid-dependent vs 18% in steroid-resistant cases) plateaued after a maximum of 6 months. In steroid-dependent cases the remission rate was in the order of 40% at 1 month, 60% at 2 months and 70% at 3 months. In only 10% of the extant patients was remission achieved by pursuing treatment up to 6 months. In other words, pursuing CsA treatment of nephrotic syndrome for longer than 6 months is of no avail in terms of efficacy and greatly increases the risk of renal toxicity, especially in FSGS.

CsA dependency was observed from the very first trials of treatment, where results were usually published at 1 year [23]. Tapering the drug to a stop after complete remission resulted in 50% recurrence of nephrotic syndrome within 2 months. The probability of remaining in remission after abruptly stopping CsA was 50% at 2 months, 30% at 4 months, 20% at 6 months and nil at 9 months. This left the prescribing nephrologist with the disquieting prospect of indefinite treatment with a nephrotoxic drug, hence trading extrarenal steroid toxicity for renal CsA toxicity. However, the notion of CsA dependency was partly reconsidered when we analysed a series of 36 adults, selected among the 150 cases of the Société de Néphrologie trial and having undergone repeat renal biopsies after 1–5 years of CsA treatment [14]. Fourteen out of 36 had been treated for 26 ± 14.5 months (10 with MCD and four with FSGS). After a long period of remission, CsA was very progressively tapered to a stop, and in these 14 patients remission was durable and maintained without steroids in 11 and with low-dose steroid treatment in three. At the time of writing this, the longest follow-up starting at the end of CsA treatment is in the order of 12 years. These findings lead us to reconsider the concept of CsA dependency, at least in MCD. It is worth citing publications dating from the time when no treatment of nephrosis, be it immunosuppressive or corticosteroid therapy, was available. In those days 40% of patients who had survived the complications of nephrotic syndrome might enter spontaneous remission within 5 years. In view of this natural history of untreated nephrosis, it can be assumed that in a substantial number of cases the suppressive effect of CsA on the process responsible for nephrotic syndrome buys time to reach the phase of extinction of the disease.

However, in ~20% of the cases, very slow tapering of CsA dosage after 1 year showed that, although CsA-dependent, these patients remained free of proteinuria with extremely low dosages, < 3 mg/kg/day, and even in one case with 1 mg/kg/day. In such cases CsA dependency to a very low dosage most probably entails very little risk of toxicity over years and maybe decades.

Randomized trials

In 1988, Garin et al. [26] carried out an 8-week controlled crossover trial of CsA in eight children with steroid-resistant nephrotic syndrome. They found no significant changes during the short period of CsA treatment.

In 1991, Tejani et al. [27] randomized 28 nephrotic children to determine the efficacy of an 8-week treatment course of low-dose prednisone and CsA vs high-dose prednisone. Thirteen out of 14 children receiving combined therapy underwent remission vs eight of 14 receiving prednisone alone.

In 1992, Niaudet [28] randomly assigned 40 children with steroid-dependent nephrosis and steroid toxicity to receive either CsA for 3 months and tapering doses over the following 3 months, or chlorambucil at a cumulative dose of 8 mg/kg. Of 20 patients treated with CsA, four relapsed before or on discontinuation of prednisone, seven relapsed when the initial dose of CsA was tapered and eight after CsA withdrawal. Of the 20 patients treated with the alkylating agent, 14 relapsed whereas six were still in remission 27–49 months after completion of treatment. Thus, the actuarial remission rate at 2 years was 45% after chlorambucil and only 5% after a 3-month course of CsA. Niaudet concluded that children with steroid-dependent nephrosis should be treated with chlorambucil before resorting to CsA. It should be noted that the long-term consequences of chlorambucil on male fertility were unknown.

In 1993, Ponticelli et al. [29] carried out a multicentre study of CsA for 1 year vs cyclophosphamide for 8 weeks in patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome. Corticosteroid treatment was continued during the study period. At 2 years, 25% of the patients in the CsA subset and 63% of those in the cyclophosphamide group had not experienced relapse of nephrotic syndrome. Tolerance of both drugs was considered good. They reported that out of 66 patients followed up for 3–24 months after randomization at 9 months, 26 of 35 CsA treated patients were in complete remission and a further five were in partial remission; 18 of 28 cyclophosphamide-treated patients were in complete remission and one in partial remission. This study confirmed that durable remission of nephrotic syndrome is more often obtained with an alkylating agent than with CsA. However, it also confirms the above personal observations that patients with idiopathic nephrotic syndrome treated with CsA are not
necessarily CsA-dependent, as one-fourth enjoyed stable remission after discontinuation of this immunophilin modulator.

In 1993 the same team carried out a randomized trial of CsA in steroid-resistant idiopathic nephrotic syndrome in 40 patients [30]. The remission rate of nephrotic syndrome during the first year was 13 of 22 in CsA-treated patients vs 13 of 19 in controls. No significant changes in blood pressure and renal function were observed between the CsA and the control group. The authors concluded that CsA could bring about remission in some 60% of patients with steroid-resistant idiopathic nephrotic syndrome.

In 1996, Lieberman and Tejani [31] randomized 24 patients with primary FSGS. Twelve received CsA for 6 months and 12 were placebo treated. All patients who received CsA experienced significant reduction in proteinuria. The fractional decline in GFR over the course of the study was the same between the CsA and the placebo-treated group. The authors concluded that CsA has a favourable effect in steroid-resistant FSGS without undue toxic effects.

The most recent randomized trial of CsA was published by Cattran et al. in 1999 [32] in 49 cases of corticosteroid-resistant FSGS. This trial that compared 26 weeks of CsA plus low-dose prednisone to placebo plus prednisone. Seventy per cent of the treatment group vs 4% of the placebo group had a partial or complete remission of proteinuria by 26 weeks. Relapse occurred in 40% of the remitters by 52 weeks and 60% by week 78, but the remainder stayed in remission to the end of the observation period that lasted an average of 200 weeks. Renal function was better preserved in the CsA group, in which a 50% decrease in baseline creatinine clearance was observed in 25% compared with 52% of controls. The authors concluded that CsA is an effective treatment of steroid-resistant FSGS and preserves renal function in a significant proportion of patients.

Comments

The foregoing data leaves one with great perplexity. On one hand, overall results of open studies that deal with a substantial number of patients clearly indicate that CsA alone is particularly efficient in steroid-sensitive idiopathic nephrosis and especially in MCD, with a remission rate in the order of 80%. Conversely, the response in steroid-resistant nephrosis, especially with lesions of FSGS, is poor, in the order of 20%. In the latter subset, adding corticosteroids increases the remission rate to ~30%. However, all studies in which repeat renal biopsies were carried out to determine the renal tolerance point to increasing fibrosis, despite reassuring stable creatinine levels, and this especially in FSGS where CsA adds its nephrotoxic potential to the development of the primary renal disease. It has also been established that dosages > 5.5 mg/kg/day in adults and perhaps a little more in children entail a significant risk of nephrotoxicity. On the other hand, considering the foregoing data, one remains at a loss to understand how some randomized studies from various parts of the world indicate a high success rate, even in steroid-resistant FSGS, with stable and even improving renal function.

Tacrolimus (FK506)

The trials of treatment of nephrosis with FK506 are almost anecdotal. McCauley and co-authors treated seven cases of various glomerulopathies with tacrolimus, including four children with FSGS [17]. All four had received prednisone previously, associated with cyclophosphamide in one, a combination of cyclophosphamide and CsA in two, and CsA in one patient. The first case was resistant to treatment; the three others experienced a partial response on CsA. FK506 induced complete remission in one case and a significant decline in proteinuria with a rise in serum albumin levels in the other three. Renal function declined in all and returned towards pre-treatment values when dosage was reduced or after stopping the drug. The first case was followed up for 14 months, and two attempts to stop FK506 induced a flare in proteinuria that resolved within days of resuming the drug. This publication left the impression that similarly to CsA, FK506 may induce complete remission in some cases and fail in others. The authors speculated that differing responses to T cell-directed therapy might indicate that nephrosis with lesions of FSGS might be the consequence of various pathogenetic mechanisms.

In 1997, Schweda et al. [33] published the case of a young woman with relapsing MCN syndrome that was first CsA- and corticosteroid-dependent and then evolved to resistance to both agents. CsA was replaced by a daily dosage of 6 mg of tacrolimus. Remission followed. Prednisolone was tapered to a stop. Complete remission was maintained with a daily dosage of 4 mg tacrolimus with normal renal function and normal renal histology on repeat biopsy. The overall duration of treatment at the time of publication was 20 months.

Sirolimus (rapamycin)

Considering its lack of nephrotoxicity and its efficacy in the field of transplantation, it would be understandable that sirolimus be tried in the treatment of idiopathic nephrotic syndrome. At the time of writing a Medline search did not find a single reference on this issue. However, it is noteworthy that the Paris Necker Hospital transplantation team, which carried out a trial of sirolimus in the field of renal transplantation, observed fulminant de novo FSGS in eight patients, including only one whose primary renal disease was FSGS. Peraldi et al. presented this complication of sirolimus treatment in abstract form to the 2000 American Society of Nephrology meeting [34]. The pathophysiology of sirolimus-related FSGS is unclear. In any event, these data should lead one to be extremely cautious in considering this treatment in MCD and FSGS.
Conclusion

So far, the only immunophilin modulator for which efficacy and tolerability have been adequately studied over 15 years in the treatment of idiopathic nephrosis is CsA. Unfortunately, and for reasons that escape common sense and understanding, according to the literature, CsA might be considered as the best and the worst of drugs. From our personal experience dating back to 1985 and now amounting to some 200 cases, we would like to leave the reader with the following principles and guidelines.

First, the best indication of CsA in the treatment of idiopathic nephrosis is the patient with MCD and corticosteroid dependency with several relapses each year and corticosteroid toxicity. In such a case the success rate of CsA is in the order of 70–80%. The drug should be prescribed for 3 months before the ongoing dosage of corticosteroid is progressively tapered to a stop. After a year of treatment CsA should be very progressively tapered from 5 mg/kg/day to the lowest dosage entertaining remission. After 3 years of treatment ~25% of the patients can be progressively weaned from CsA and enjoy stable remission.

The worst indication is the patient with corticosteroid-resistant FSGS, pre-CsA vascular lesions, interstitial fibrosis and incipient renal insufficiency. This patient has < 20% chance of achieving complete remission. Partial remission does not necessarily mean that the primary glomerular disease is under control. The risk of nephrotoxicity is high. Resistance to CsA and/or rising serum creatinine levels should lead to stopping treatment after no longer than 4–5 months.

Secondly, CsA should be considered a glucocorticoid sparing agent, but this implies that steroid toxicity be traded off for nephrotoxicity. However, most studies showed that adding corticosteroids to CsA increases the remission rate from 20 to > 30%. This may be the case for some patients with nephrosis stubbornly resistant to steroids alone.

Thirdly, CsA nephrotoxicity can be limited by using dosages not > 5 mg/kg/day and by reducing dosage whenever serum creatinine level rises > 30% from baseline. Repeat renal biopsy should be carried out between 1 and 2 years of treatment even when renal function is apparently stable, in order to detect and quantify vascular and tubulointerstitial lesions, which would indicate that pursuing treatment with CsA is unreasonably hazardous to renal function.

Fourthly, it must be stressed that most data regarding tolerability of CsA therapy were based on treatment with the former presentation of the drug, that is, Sandimmune. The better bioavailability of the new presentation, Neoral [35], most probably implies that the dosage guidelines indicated above should be reconsidered and that dosages distinctly < 5 mg/kg/day should be used for avoiding renal toxicity. In fact, very low dose CsA monotherapy may be effective in the treatment of idiopathic nephrotic syndrome [36], and every effort should be applied to use this drug at the lowest possible dosage maintaining remission.

References