Treatment of nephrotic syndrome with cyclosporin A. What remains in 1994?

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Ten years after treatment of idiopathic nephrotic syndrome was undertaken with cyclosporin A, its mode of action is still unclear. The drug appears not to be merely an immunosuppressive agent, but also seems endowed with nonspecific antiproteinuric properties, explaining partial remissions observed in various aetiologies of nephrotic syndrome, including some with no immunologic background [1]. Its indications continue to generate contradictory publications. Some affirm that it is a major advance in the treatment of nephrotic syndrome, while in other publications, prophets of doom fulminate caveats against those who undertake to destroy the kidneys of their renal patients with the nephrotoxic distillate of *Tolypocladium inflatum* (Gams). This stream of articles and oral presentations leaves the nephrologist more perplexed than enlightened. What aetiologies of nephrotic syndrome are the right indications? Is success predictable in a given patient? Should cyclosporin A be used alone or be boosted by steroids? What dosage should be used? Should it be titrated by monitoring blood levels? Or just according to serum creatinine fluctuations? Will steroid dependency invariably be traded off for cyclosporin dependency? If so, how many cyclosporin-dependent patients will have to pay the price of remission with relentless renal interstitial fibrosis?

What aetiologies of nephrotic syndrome are the right indications?

Cyclosporin A has been tried in more than a dozen aetiologies of nephrotic syndrome. A common disorder afflicts the literature concerning nontransplant indications of cyclosporin A: the lack of controlled studies, which would dispel the doubt between the effect of the drug and the natural history of the glomerulopathy. Let us then forget the anecdotal reports on IgA nephropathy, Alport syndrome, Wegener's granulomatosis, amyloidosis, diabetic glomerulosclerosis and membrano-proliferative GN. Concerning lupus nephritis, the early impression given by the experience of the team in Geneva [2] was favourable. A more recent report of their experience [3] concerning an open study of 60 patients presents several subgroups having various outcomes. The steroid-sparing effect of cyclosporin A is still evident, but the statement that 'cyclosporin A is now a recognised treatment of lupus nephritis' [2] should be nuanced. Therefore, we shall concentrate on the three major indications, namely idiopathic nephrotic syndrome with no glomerular lesions (MCD), the same with focal and segmental glomerulosclerosis and idiopathic membranous glomerulopathy.

Minimal change disease

Doubtless, MCD is the best indication for cyclosporin A treatment. The present experience amounts to hundreds of cases. Studies conducted between 1986 and 1988 were analysed [4] in 112 adults and 113 children. Experience acquired since then has not changed the rates of success and failure. The best results are achieved in patients with steroid-sensitive nephrotic syndrome, including steroid-dependent and multirelapsing cases. Cyclosporin A alone, at the low dosage of 5 to 6 mg/kg/day, obtains durable remission of the nephrotic syndrome in 70–80% of cases and hence suppression of prednisone and of its toxic effects. This is especially favourable in children. Paediatricians observe regression of Cushingoid features and catch-up growth. Nephrologists caring for adults are relieved to observe disappearance of steroid-induced diabetes and to remove a cause of hip osteonecrosis. Such favourable effects of cyclosporin A are obtained in patients whose nephrotic syndrome had not gone into remission with a previous course of cytotoxic agents. Regression of proteinuria is slow, and in 80–90% of cases takes up to 4 months. Remission is dosage-dependent, and within the first year of treatment attempts to reduce it below 5 mg/kg/day are usually followed by reappearance of proteinuria, which again regresses after resuming the previous regimen. Stopping treatment within the first year is almost constantly followed by a flare-up of nephrotic syndrome, indicating cyclosporin dependency.

In contrast, the success rate in steroid-resistant forms is in the order of only 20–30%. It is slightly improved by the addition of corticosteroids, but then the steroid-
sparing effect of cyclosporin A, which is its best justification, is lost. As specified above, failure of cyclosporin A can be pronounced when remission has not been obtained within 4, and a maximum of 6 months. In this case continuing treatment is useless and hazardous.

Focal-segmental glomerulosclerosis

The results of cyclosporin A treatment of focal segmental glomerulosclerosis are rather disappointing. The success rate is in the order of 20–30%, mostly in patients with steroid-sensitive forms. Discrepancies are apparent among publications. In some [5], cyclosporin A obtained, at best, partial remission of the nephrotic syndrome but surveillance of renal function and repeat renal biopsies often showed that the glomerular lesions continued to develop, that tubulointerstitial damage progressed and that patients evolved to progressive renal failure. The respective parts played by the natural history of the primary renal disease and by cyclosporin A nephrotoxicity were difficult to distinguish. Some investigators claimed that cyclosporin A accelerates the course of focal segmental glomerulosclerosis to end-stage renal failure. A recent randomised trial in steroid-resistant idiopathic nephrotic syndrome included fourteen patients with focal segmental glomerulosclerosis in the cyclosporin A arm [6]. In three, complete remission and in four partial remission were obtained with cyclosporin A alone. No significant changes in renal function were noted at the time when treatment was tapered to a stop, but this was at one year, and repeat renal biopsies were not done.

The Collaborative Group of the Société de Néphrologie enrolled 98 patients with steroid-resistant or -dependent idiopathic nephrotic syndrome, including 46 with focal segmental glomerulosclerosis [5]. The rate of remission was only 20% in steroid-resistant focal segmental glomerulosclerosis. Fourteen patients with an initial diagnosis of focal segmental glomerulosclerosis were followed-up for 7–78 months (16.4 ± 11.6) and in each case repeat renal biopsy was carried out at end-point [7]. In these patients, the post-cyclosporin A renal function had declined.

Repeat renal biopsy showed significant aggravation of glomerular lesions, even in patients in whom cyclosporin A had obtained complete or partial remission. A marked increase in interstitial fibrosis was observed, especially in patients who initially had a higher percentage of glomeruli with lesions of focal segmental glomerulosclerosis and already abnormal renal function, and who received > 5.5 mg/kg cyclosporin A per day. Niaudet's group carried out repeat biopsies in nephrotic children treated with cyclosporin A [8] and stressed the discrepancy between apparently stable renal function and steady increase in interstitial fibrosis indices with time. Thus, partial and, rarely, complete remission can be achieved with cyclosporin A in steroid-resistant focal segmental glomerulosclerosis, but the risk of deterioration of renal histology and, later, renal toxicity is high.

Is success predictable in a given patient?

Previous response to corticosteroids is best predictive of remission, irrespective of glomerular lesions (i.e., MCD or focal segmental glomerulosclerosis). However, there are patients with steroid-resistant focal segmental glomerulosclerosis in whom remission is achieved with cyclosporin A and cases of steroid-dependent MCD in whom it is of no avail. So far, no reliable criterion has been found to anticipate success or failure. Nevertheless, in terms both of remission and of nephrotoxicity, it has been established that patients with focal segmental glomerulosclerosis plus tubulointerstitial lesions and incipient renal insufficiency are at high risk of treatment failure. Even when cyclosporin A induces partial remission, the drug (and/or the spontaneous development of the primary renal disease) leads to rapidly progressive renal insufficiency and probably precipitates the course to maintenance haemodialysis. Careful analysis of a recent pre-cyclosporin A renal biopsy is therefore mandatory before embarking on cyclosporin A treatment in such patients.

Also, it is clear that the risk of nephrotoxicity is directly proportional to dosage. The 'cut-off' between patients with stable renal function and patients with progressive interstitial fibrosis is 3.5 mg/kg/day, irrespective of whole blood levels during treatment [7]. This means that monitoring of cyclosporin A blood levels is not mandatory here. Conversely, meticulous surveillance of serum creatinine levels is essential. A persisting rise of 30% over baseline should lead to dosage reduction. Declining GFR requires stopping treatment. Even when renal function is stable, many consider that repeat renal biopsy after one year is recommendable to verify that smouldering interstitial fibrosis is not at work.

Idiopathic membranous glomerulopathy

Until 1991, 77 cases of idiopathic membranous glomerulopathy had been treated with cyclosporin A in open trials. The results were complete remission in 20%, partial remission in 46% and failure in 34%, not very different from those observed in large series dealing with the natural history of untreated idiopathic membranous glomerulopathy. Catrnan et al. [9] recently presented a controlled trial of cyclosporin A versus placebo in 17 patients with idiopathic membranous glomerulopathy, steady decline of renal function, and persistent nephrotic proteinuria. The eight cyclosporin A-treated patients showed both improvement in proteinuria and a slowed rate of decline of GFR after a 12-month treatment. Six of them retained this improvement in creatinine clearance and proteinuria over a post-medication period of 5 to 14 months.
Although small, this first controlled trial substantiates the conclusion that 'cyclosporin A appears to be an effective and acceptable therapy in patients with an established, progressive membranous nephropathy.' However, controlled studies in larger series are eagerly awaited.

Is cyclosporin dependency inevitable?

As mentioned above, stopping cyclosporin A within the first year of successful treatment usually leads to relapse of nephrotic syndrome, which is a major concern for the nephrologist faced with the prospect of indefinitely maintaining treatment with a potentially nephrotoxic drug. A collaborative registry of patients treated in France and neighbouring countries, some of them since 1985, offered the opportunity of re-evaluating the long-term follow-up of 36 adult cases, whose trace had often been lost after the first year of treatment [7]. A rewarding outcome of the enterprise was to discover that in 14 patients, who had been treated with cyclosporin A for 26 ± 14.5 months (12–60), cyclosporin A had been tapered to a stop and they remained in remission, 11 without steroids and 3 with low-dose steroid treatment. The follow-up of these patients who escaped cyclosporin A dependency now ranges from 9 months to 6 years. This indicates that patients whose nephrotic syndrome responds to cyclosporin A are not inescapably destined to indefinite exposure to the drug. It might be hypothesized that in some instances cyclosporin A smothers the ill-identified process which induces nephrotic proteinuria, tiding the immune system over until the activity of the disease has burnt out.

What remains of idiopathic nephrotic syndrome treatment with cyclosporin A in 1994? More than encouraging results, new promising indications, well-defined guidelines and, last but not least, the notion that cyclosporine dependency is not ineluctable.

References