Cyclosporine in the Treatment of Idiopathic Nephrotic Syndrome

Alain Meyrier
Hôpital Européen Georges Pompidou and INSERM U 430, Paris, France

Two years after the marketing of cyclosporine A (CsA) in the field of organ transplantation the molecule was tried in idiopathic nephrotic syndrome (INS).The first trials were conducted by Meyrier et al in adults [18] and by Tejani et al in children [35] and followed by a few letters on this new treatment mode of INS [10, 14]. The first results were presented at the 18th Annual Meeting of the American Society of Nephrology and published, respectively in the British Medical Journal [19] and in Kidney International [36].

The rationale for treating INS with CsA was rather fragile. It had been established that CsA impairs the production of IL-2 and of γ interferon. At this time, the prevailing hypothesis (the "Shalhoub hypothesis") [34] was that INS was caused by a lymphokine that diminished the negative, anionic charges of the filtration barrier, especially those present on the glomerular basement membrane (GBM), this polyanion repulsing the negatively charged albumin molecules and hampering their egress into the urinary chamber [14; 39; 13; 33].

Soon after the first trials, which raised considerable interest, several investigators tried the effect of CsA in various glomerulopathies. Some, like systemic lupus erythematosus were undoubtedly immunologic in nature. Favre et al, [8] studied the effect of CsA in lupus nephritis and obtained very favorable results. Regrettably no further trials of CsA have been conducted in this indication. Other trials were undertaken in glomerulopathies of immunologic origin, such as membranous glomerulopathy [6], IgA nephropathy [15], proliferative GN, Schönlein-Henoch purpura [3], Wegener's granulomatosis [2, 7, 9], crescentic glomerulopathies [32] and recurrent or de novo post-transplantation GN. However some trials were done in glomerulopathies with obviously no immunological basis, such as Alport's syndrome [4] and diabetic glomerulopathy [20, 21]. As early as in 1989 a review of the literature [21] retrieved 538 patients treated with CsA for such disparate diseases. On the whole, it was observed that, irrespective of the immunologic or non-immunologic nature of the disease, CsA obtained a significant reduction of proteinuria [23, 27].

Mode of action

The mode of action of cyclosporine A (CsA) in idiopathic nephrotic syndrome (INS, or "nephrosis"), that is minimal change disease (MCD) and focal-segmental glomerulosclerosis (FSGS) appears to be both immunologic and pharmacologic.

CsA significantly reduces proteinuria in a wide variety of non-immunologic glomerular diseases. Diminution of proteinuria simply by the renal vasoconstrictive action of CsA is not a fully satisfactory explanation. In vitro study of glomerular permeability to albumin, animal experiments and sieving curves of dextran infusion in man demonstrated that CsA exerts an antiproteinuric effect by reducing glomerular membrane permeability to albumin through increased charge selectivity [12, 1, 40, 41, 24] This notion must be kept in mind when interpreting cases of partial remission induced by CsA.

Efficacy and tolerability

The first trials of CsA (Sandimmune) treatment of nephrosis, reported between 1986 and 1988, (For review see [21]) were followed by numerous contributions which confirmed that response is essentially predicted by previous response to corticosteroid treatment, and that CsA nephrotoxicity is low when dosage does not exceed 5.5 mg/kg/d. [20, 21, 23-25, 28, 27]. It is important to stress that, considering the better biodisponibility of Neoral the dosage should be reduced by 30% for similar efficacy. Until further studies provide information on the recommended dosage of Neoral in the treatment of idiopathic nephrotic syndrome, 3 mg/kg/day should be considered a maximum.

Children

Corticosteroid - sensitive nephrosis. The best indication of CsA is the patient with steroid-responsive nephrosis in whom steroid dependency or a multirelapsing course induces steroid toxicity.

Niaudet and Habib [27] reviewed the results of CsA treatment in 129 children with steroid-sensitive or -dependent INS. CsA obtained complete remission in 109 (84.5%). Tejani et al. [36, 37], using CsA as first-line treatment, obtained remission in 13/14 children, compared with 8/14 children receiving prednisone alone. In most studies, dosage of Sandimmune in children was in the order of 6 mg/kg/day. However, Ingulli and Tejani [11], analyzing the results of a 2-month treatment in 47 children, identified 13 nonresponders whose serum cholesterol levels were significantly greater than in responders. Increasing dosage to 10-14 mg/kg body weight, they obtained remission without evidence of nephrotoxicity. Lieberman and Tejani [16] in a randomized, double blind placebo-controlled trial included 25 patients with a mean age just over 11 years who were treated for 6 months. All of the 12 patients who received CsA experienced a significant reduction in proteinuria, as opposed to only 2 / 12 in the placebo subset. A significant correlation was found between the percentage of change in proteinuria and the pre-study serum cholesterol levels. Ten

Correspondence to: Alain Meyrier, Hôpital Européen Georges Pompidou and INSERM U 430, Paris,
e-mail: alain.meyrier@brs.ap-hop-paris.fr

patients were continued on CsA in doses ranging from 6 to 12 mg/kg/day, and maintained normal renal function.
CsA induces remission of nephrotic syndrome in about 80% of steroid-sensitive cases. It allows suppression or drastic reduction in corticosteroid needs, with regression of steroid toxicity, but contrary to alkylating agents [28], most children relapse when dosage is tailed off to a stop, which means that CsA exerts a suspensive, not a curative effect on the process responsible for INS. This raises the question of CsA nephrotoxicity following prolonged exposure. Niaudet et al. [30] and Melocoton et al. [17] studied long-term tolerance in CsA-dependent children. Serial renal biopsies disclosed increasing interstitial fibrosis despite apparently stable renal function. Such findings illustrate the importance of repeat renal biopsy when a patient responds to CsA but remains CsA dependent for a long period of time.

Corticosteroid-resistant INS

The results of CsA treatment in steroid-resistant forms are less satisfactory. Niaudet and Habib [27] reviewed 8 uncontrolled studies involving 60 steroid-resistant patients. Complete remission was attained in only 12 (20%). In the U.S., Melocoton et al. [17] treated 18 patients with steroid-resistant nephrotic syndrome and steroid-dependent nephrotic syndrome for 2 to 29 months. CsA did not obtain remission in ten patients with steroid-resistant INS, regardless of the presence of FSGS or MCD on renal biopsy. Following 11 to 29 months of CsA, 7 patients underwent renal biopsy, which showed nephrotoxicity in all 7 and led to stopping CsA in 4. The association of CsA and low-dose prednisone significantly improves results. Niaudet et al [27] prospectively studied 65 children treated with a combination of CsA and prednisone for 5 months: 42% went into complete remission, 6% into partial remission and 52% failed to respond. The longest time to remission was 6 months. Eight patients who relapsed after CsA treatment responded further to prednisone alone, and 9 patients had not relapsed more than one year after CsA withdrawal.

Adults

The results in adult INS are comparable to the foregoing data in children (for review, see Meyrier, [20, 21]). This is reflected by the study of the French Collaborative Group of the Société de Néphrologie [22-24]. It enrolled 112 patients, among whom 98 were considered valid for evaluating efficacy. There were 52 cases with MCD and 46 with FSGS; 37/98 (38%) were steroid-dependent and 61/98 (62%) were steroid-resistant. Of 52 patients with MCD, 36 (69.23%) went into remission and 16 (30.76%) were failures. Of 46 patients with FSGS, 11 (24%) underwent remission and 35 (76%) failed to respond. The rate of remission was highest in steroid-dependent MCD (71%) and lowest in steroid-resistant FSGS (20%). Ponticelli et al [31] confirmed the lower remission rate of CsA treatment of steroid-resistant adult INS. In 12 adults, including 10 with FSGS and 2 with MCD they obtained partial remission in 7 and 5 were failures.

Tolerance was analysed by Meyrier et al. [25]. Minor side effects were common but led to withdrawal in less than 10% of cases. Renal tolerance was evaluated on the basis of renal function tests and in 36 cases on repeat renal biopsies. Renal function and histology were remarkably stable in patients with MCD. Conversely, when renal biopsy disclosed FSGS, tubulointerstitial lesions which were already present on pre-CsA biopsies increased with time, along with declining renal function. This was interpreted as a combination of drug toxicity and the natural history of the primary renal disease. Multivariate analysis identified three predictive factors of CsA toxicity: FSGS with accompanying tubulointerstitial injury, incipient renal insufficiency with serum creatinine levels > 180 mmol/L and CsA dosage > 5.5 mg/kg/day. Aggravation of interstitial fibrosis and of FSGS was observed in some cases in which CsA had obtained partial or even complete remission, again indicating the necessity of repeat renal biopsies in patients so treated. An encouraging finding was that in 14/36 adults who had been treated with CsA for steroid-dependent or -resistant INS during 26 ± 14.5 months, tailing off CsA to a stop was followed by stable remission, indicating that CsA dependency is not the rule. In a series of 112 patients enrolled in the open trial of the "Société de Néphrologie" 25% of responders remained in stable remission after tapering CsA to a stop. The same was observed in children by Yoshikawa et al. [38]. Time to remission The time to remission in CsA-responsive INS was analysed [5, 24] by pooling data from 7 studies including 104 steroid-dependent and 226 steroid-resistant patients, both children and adults. The cumulative rate of complete remission in steroid-dependent cases was in the order of 60% at 2 months, 75% at 3 months, reached 80% at 6 months, and thereafter increased very little. The same type of progression was observed in steroid-resistant cases, where the maximum cumulative rate of remission (20%) was achieved at 6 months. These figures indicate that failure of CsA can be pronounced at 6 months of treatment, provided dosage has been adequate, that is, not less than 5 mg/kg/day.

Conclusions and perspectives

Cyclosporine is now a recognised treatment of idiopathic nephrotic syndrome. Considering its lack of cytotoxic effects, and especially its very limited risk of opportunistic infections and of sterility in the male, it appears to have acquired a place of choice versus alkylating agents in the treatment of corticosteroid dependent or resistant nephrosis. Renal toxicity can be limited by careful selection of patients and meticulous monitoring of renal function. Repeat renal biopsy after 12 to 18 months of treatment should reduce the hazards of drug toxicity in CsA dependent cases. In all cases its major advantage is the reduction or suppression of corticosteroid treatment. In some selected cases, such as the diabetic and the obese, it may be considered as a first line treatment. Finally, contrary to early publications CsA dependency is far from being the rule, and a substantial number of patients may remain in remission after tapering treatment to a stop.

References

1. Berden JHM, Schrijver G, Desassis JF, van den Born J: Cyclosporine A (CsA) in experimental models of proteinuria. Proceedings of the XIIth International Congress of Nephrology, Jerusalem, June 1993, (abstract) p. 534
2. Borleffs JCC, Derksen RHWM, Hene RJ: Treatment of Wegener's granulomatosis with cyclosporine A. Ann Rheum Dis, 1987; 46:175
3. Brodehl J, Brandis M, Helmchen U. Cyclosporin A treatment in children with minimal change nephrotic syndrome and focal-segmental glomerulosclerosis Klin Wochenschr 1988; 66:1126-37
4. Chen D, Jefferson B, Harvey SJ et al. Cyclosporine A slows the progressive renal disease of Alport syndrome (X-linked hereditary nephritis): results from a canine model. J Am Soc Nephrol. 2003; 14:690-8
5. Collaborative Study Group of Sandimmun in Nephrotic Syndrome: Safety and tolerability of cyclosporin A (Sandimmun) in idiopathic nephrotic syndrome. Clin Nephrol 1991; 35(suppl 1):S48-S60
6. De Santo NG, Capodicasa G, Giordano C. Treatment of idiopathic membranous nephropathy unresponsive to methylprednisolone and chlorambucil with cyclosporin. Am J Nephrol 1987; 7:74-6
7. Dupont JL, Humbert P, de Wazières B. Intérêt de la ciclosporine dans le traitement de la maladie de Wegener. Presse Méd. 1988; 17:1764-5
8. Favre H, Miescher PA, Huang YP, Chatelanat F, Mihatsch MJ Ciclosporine in the treatment of lupus nephritis Am J Nephrol 1989; 9 (suppl 1) 57-60
9. Gremmel F, Druml W, Schmidt P, Graninger W. Cyclosporine in the treatment of Wegener granulomatosis. Ann Int Med 1988; 108:491
10. Hoyer PF, Krull F, Brodehl J: Cyclosporine in frequently relapsing minimal-change nephrotic syndrome. Lancet 1986; 2:335
11. Ingulli E, Tejani A: Severe hypercholesterolemia inhibits cyclosporin A efficacy in a dose-dependent manner in children with nephrotic syndrome. J Am Soc Nephrol 1992; 3:254-9
12. Jameson MD, Savin VJ, Sharma R, Lovell HB, Diederich DA: Cyclosporine treatment decreases glomerular ultrafiltration coefficient. Proceedings of the National Kidney Foundation . 19th Annual Scientific Meeting, Washington DC, 1989; Abstract A 12
13. Koyama A, Fujisaki M, Kobayashi M, Igarashi M, Narita M: A glomerular permeability factor produced by human T cell hybridomas. Kidney Int 1991; 40:453-60
14. Lagrue G, Laurent J, Belghiti D, Robeva R: Cyclosporin and idiopathic nephrotic syndrome. Lancet 1986; 2:692-3
15. Lai KM, Lai FM, Li PKT, Vallance-Owen J: A short-term controlled trial in IgA nephropathy. Transpl Proceedings, 1988; 20 (suppl 4) 297-303
16. Lieberman KV, Tejani A: A randomized double-blind placebo-controlled trial of cyclosporine in steroid-resistant idiopathic focal segmental glomerulosclerosis in children. J Am Soc Nephrol 1996; 7:56-63
17. Melocoton TL, Kamil ES, Cohen AH, Fine RN: Long-term cyclosporine A treatment of steroid-resistant and steroid-dependent nephrotic syndrome. Am J Kidney Dis 1991; 18:583-8
18. Meyrier A, Simon P, Perret G, Condamin MC: Cyclosporin in lipoid nephrosis and focal-segmental hyalinosis resistant to other treatments. Proceedings of the 18th Annual Meeting of the American Society of Nephrology, 1985, p. 48A (abstract)
19. Meyrier A, Simon P, Perret G, Condamin-Meyrier MC: Remission of idiopathic nephrotic syndrome after treatment with cyclosporin A. Brit Med J 1986; 292:789-92
20. Meyrier A, Collaborative group of the Société de Néphrologie Ciclosporin in the treatment of nephrosis: Am J Nephrol 1989; 9: (Suppl 1):65-71
21. Meyrier A: Treatment of glomerular disease with cyclosporin A. Nephrol Dial Transpl 1989; 4:923-31
22. Meyrier A, Condamin MC, Broneer D, The Collaborative Group of the French Society of Nephrology: Treatment of adult idiopathic nephrotic syndrome with cyclosporin A: minimal-change disease and focal-segmental glomerulosclerosis. Clin Nephrol 1991; 35: (Suppl.1):S37-S42
23. Meyrier A: Antiproteinuric and immunologic effects of cyclosporin A in the treatment of glomerular diseases. Nephrol Dial Transpl 1992; S1:80-4
24. Meyrier A, Niaudet P, Brodehl J: Optimal Use of Sandimmun in Nephrotic Syndrome (monograph). Berlin, Springer-Verlag, 1992, pp 1-34 (monograph)
25. Meyrier A, Noël LH, Auriche P, Callard P: Long-term renal tolerance of cyclosporin A treatment in adult idiopathic nephrotic syndrome. Kidney Int 1994; 45:1446-56
26. Meyrier A: Use of cyclosporin in the treatment of idiopathic nephrotic syndrome in adults, in Tejani A (ed): Cyclosporin in the Therapy of Renal Disease, Karger, Basel, 1995, pp 28-48
27. Niaudet P and Habib R: Cyclosporine in the treatment of idiopathic nephrosis. J Am Soc Nephrol, 1994; 5: 1049–56
28. Niaudet P, French Society of Pediatric Nephrology: Comparison of cyclosporine and chlorambucil in the treatment of steroid-dependent idiopathic nephrotic syndrome: a multicenter randomized controlled trial. Pediatric Nephrol 1992; 6:1-3
29. Niaudet P, Habib R: Cyclosporine in the treatment of idiopathic nephrosis. J Am Soc Nephrol 1994; 5:1049-56
30. Niaudet P, Broyer M, Habib R: Serial renal biopsies in children with idiopathic nephrosis receiving cyclosporin, in Tejani A (ed): Cyclosporin in the Therapy of Renal Disease, Karger, Basel, 1995, pp 78-83

31. Ponticelli C, Rizzoni G, Edefonti A et al.: A randomized trial of cyclosporine in steroid-resistant idiopathic nephrotic syndrome. Kidney Int 1993; 43:1377-84
32. Sadadji SA, Shah RM: Successful treatment of immune complex mediated rapidly progressive glomerulonephritis (IG-RPGN) with cyclosporine A. Intern Congress of Nephrology, London, 1987; 90: abstract
33. Sewell RF, Short CD: Minimal-change nephropathy: How does the immune system affect the glomerulus? Nephrol Dial Transpl 1993; 8:108-12
34. Shalhoub RJ: Pathogenesis of lipoid nephrosis: a disorder of T cell function. Lancet 1974;ii:556-9
35. Tejani A, Butt K, Khawar R, Suthanthiran M, Rosenthal CJ, Trachtman H, Fusi M: Cyclosporine (CY) induced remission of relapsing nephrotic syndrome (RNS) in children. Proceedings of the 18th Annual Meeting of the American Society of Nephrology, 1985 p. 57A (abstract)
36. Tejani A, Butt K, Trachtman H, Suthanthiran M, Rosenthal CJ, Khawar R: Cyclosporine A induced remission of relapsing nephrotic syndrome in children Kidney Int 1988; 33:729-34
37. Tejani A, Suthanthiran M, Pomerantz A: A randomized controlled trial of low-dose prednisone and ciclosporine versus high-dose prednisone in nephrotic syndrome of children. Nephron 1991; 59:96-9
38. Yoshikawa N, Tanaka R, Kitano Y, Nakamura H, Ito H: Long-term cyclosporin in steroid-dependent nephrotic syndrome, in Tejani A (ed): Cyclosporin in the Therapy of Renal Disease, Karger, Basel, 1995, pp 19-27
39. Yoshizawa N, Kusumi Y, Matsumoto K, Oshima S, Takeuchi A: Studies of a glomerular permeability factor in patients with minimal-change nephrotic syndrome. Nephron 1989; 51:370-6
40. Zietse R, Wenting GJ, Kramer P, Mulder Schalekamp MADH, Weimar W: Contrasting response to cyclosporin in refractory nephrotic syndrome. Clin Nephrol 1989; 31:22-5
41. Zietse R, Wenting GJ, Kramer P, Schalekamp MADH, Weimar W: Effects of cyclosporin A on glomerular barrier function in the nephrotic syndrome. Clin Sci 1992; 82:641-50