This manuscript is intended to review the current experience on the therapeutic effects of cyclosporine (CsA) in steroid sensitive idiopathic nephrosis, in steroid resistant idiopathic nephrosis and the potential nephrotoxicity of this drug.

**Therapeutic Effects of CsA in Steroid Dependent Idiopathic Nephrosis**

The first reports concerning the use of CsA in steroid sensitive and steroid idiopathic nephrosis came in 1986 from Hoyer et al. (1) who found that CsA treated patients had fewer relapses and therefore needed less steroids. Since 1986, there have been a number of uncontrolled studies showing that CsA was efficient in 75 to 90% of cases (2-10). In Necker-Enfants-Malades Hospital in Paris, we treated 45 steroid dependent children and 36 of them either went into remission or did not relapse while receiving full-dose CsA despite the fact that prednisone had been withdrawn (7). CsA was ineffective in 2 patients. The remaining 7 patients relapsed on withdrawal of prednisone treatment, but the association of CsA with low-dose prednisone allowed remission to be maintained. Prolonged CsA treatment of steroid dependent children who had a reduction of growth velocity was shown to be associated in most patients with a catch-up growth and a disappearance of Cushing features. Furthermore, in pubertal patients in whom steroid therapy is particularly deleterious to the pubertal spurt, CsA was of great help (11).

Most patients, in the published series, experienced relapses of the nephrotic syndrome when the dose of CsA was tapered or when the drug was withdrawn. The patients thus behave with CsA in the same way they used to behave with steroids, i.e. they become CsA dependent. The relapse rate usually returns to the pretreatment frequency. In our experience, the treatment has often been less effective during subsequent treatment course in children who were restarted on CsA after discontinuation of the drug. Such patients were successfully treated by a combination of CsA and low dose alternate day prednisone therapy (7).

The French Society of Pediatric Nephrology compared CsA at the dose of 6 mg/kg body weight/day for 3 months then tapered over 3 months, with chlorambucil given for 2 months to a total non-gonadotoxic dose of 8 mg/kg in children with steroid dependent idiopathic nephrosis (12). Twenty patients

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were prospectively randomized in each group. At latest follow-up, after 21 to 42 months, 30% of the patients who had received chlorambucil and only 5% of those who had received CsA were still in remission.

Ingulli and Tejani (13) recently reported that severe hypercholesterolemia may inhibit CsA efficacy. Among 47 children who received CsA at a dose of 6 mg/kg for 2 months, 13 failed to respond. These patients had a higher serum cholesterol level than the ones who responded and this feature was the only significant predictor of CsA responsiveness. Seven of the 13 non responders were retreated with higher doses of CsA (10-14 mg/kg) and five of them responded to the treatment without evidence of nephrotoxicity.

**Therapeutic Effects of CsA in Steroid Resistant Idiopathic Nephrosis**

CsA has been used in patients with steroid resistant idiopathic nephrosis with poor results. In children, eight uncontrolled studies involving 60 steroid resistant patients reported complete remission in 12 of them (2-4,6,7,14-16). The Collaborative Study Group of Sandimmun in Nephrotic Syndrome analyzed the pooled data from seven clinical studies(17). Of the 226 steroid resistant patients, 19% achieved complete remission and 18% partial remission. The rate of complete and partial remissions was significantly higher when CsA was administered in combination with prednisone. Complete remission occurred in 24% of patients treated with CsA combined to low dose prednisone and in 14% of patients receiving CsA alone.

The French Society of Pediatric Nephrology performed a prospective trial involving 65 children who received CsA (150-200 mg/m^2/day) in combination with low dose prednisone (30 mg/m^2/day) for one month and the same dose on alternate day, thereafter, for 5 months. Forty two per cent patients went into complete remission and 6% had partial remission, whereas 52% failed to respond to the treatment. Proteinuria disappeared within the first month of treatment in half of the patients who entered into complete remission. Interestingly, 8 patients who relapsed following CsA treatment further responded to prednisone and experienced a steroid dependent course. Nine patients had not relapsed 13 to 35 months after CsA withdrawal. Furthermore, at latest follow-up, only 2 patients had a persistent nephrotic syndrome and all patients had a normal glomerular filtration rate. The rapidity of the response following initiation of therapy makes it likely that the treatment was responsible for the remission, although a spontaneous remission cannot be excluded. Among the 34 patients who failed to respond to the treatment, 5 went into complete remission after the treatment had been stopped, one of them after having received a course of alkylating agents and the other 4 while receiving only supportive therapy. At latest examination, two patients were in partial remission and ten had a persistent nephrotic syndrome associated with moderate renal insufficiency in 5. Twelve unresponsive patients progressed to terminal renal failure. Lastly, four patients achieved partial remission which was transient and cessation of therapy was accompanied by an increase in proteinuria.
It is of interest that the response to CsA of patients with idiopathic nephrosis is better correlated with the initial steroid responsiveness than with the histopathologic categories. The pooled data from seven uncontrolled studies showed that the rate of remission was 60% in patients with minimal change disease (MCD) and 20% in patients with focal segmental glomerulosclerosis whereas 80% of the steroid dependent and 19% of the steroid resistant achieved complete remission.

**CsA nephrotoxicity**

The main unwanted effect of CsA is nephrotoxicity which is related to a reduced renal blood flow should be differentiated from chronic nephrotoxicity. This so-called functional toxicity does not usually lead to a permanent kidney damage. In patients with steroid dependent idiopathic nephrosis receiving CsA, a transient renal insufficiency often occurs during a relapse.

Several reports indicate that the protracted use of CsA may be associated with chronic renal injury, even in patients with normal renal function suggesting that the only reliable way of evaluating chronic CsA nephrotoxicity is to investigate the structural damage to the renal parenchyma. We compared post-treatment renal biopsies with pretreatment biopsies in a group of 42 patients with idiopathic nephrosis who had received CsA for periods ranging from 4 to 63 months. The evaluation of nephrotoxicity was based on the severity of tubulointerstitial lesions rather than on the presence of arteriolar lesions since ten of the 42 patients examined showed non-specific arteriolar lesions characterized by subendothelial widening with or without hyaline deposits but none showed the so-called CsA-associated arteriolopathy. We arbitrarily graded the tubulointerstitial changes into 3 categories according to their severity. Grade I was considered when there were no significant changes of the renal parenchyma or when occasional scattered tubules with thickened basement membranes were present. Grade II was diagnosed when the biopsy showed several small foci of atrophic tubules with thickened basement membranes within stripes of interstitial fibrosis and grade III when confluent or extensive areas of interstitial fibrosis with atrophic and/or collapsed tubules were observed. The post-treatment biopsies showed grade I lesions in 18 patients, grade II in 15 patients and grade III in 9 patients.

The interpretation of tubulointerstitial lesions in patients with idiopathic nephrosis is hazardous since one cannot exclude that the changes observed are not related to the possible progression of the disease itself particularly if lesions of focal segmental glomerulosclerosis are present. In our study, 9 of the 15 children who developed grade II tubulointerstitial damage had MCD on both pre and post-treatment biopsies, suggesting that the lesions observed are possibly related to CsA. More interestingly, the 9 patients who showed grade III tubulointerstitial lesions in the latest biopsy specimen obtained had MCD. We interpreted these rather severe tubulointerstitial changes with normal or nearly normal glomeruli as indicative of CsA nephrotoxicity.

It has been suggested that the development of CsA associated chronic
nephropathy is dose dependent (6,7). Therefore, the starting dose of CsA should not exceed 150 mg/m²/day in children. In our experience, there was no correlation between the severity of tubulointerstitial lesions and neither the mean CsA dose administered nor the trough CsA blood levels. Although the severity of tubulointerstitial damage was not correlated with the duration of CsA therapy, our study showed that tubulointerstitial lesions may increase with time. On latest evaluation, all our patients had normal glomerular filtration rate including the 9 patients with grade III tubulointerstitial lesions. The lack of correlation between rather severe structural damage and renal function indicates that the evaluation of glomerular filtration rate is, therefore, not a reliable index to predict the development of chronic CsA nephrotoxicity.

Conclusion

CsA is a good alternative to steroids in the treatment of idiopathic nephrosis especially in steroid dependent patients who develop serious side effects of steroid therapy. Most patients, however, relapse when CsA is tapered or when the treatment is withdrawn. CsA is often less effective when the treatment is discontinued and restarted later. Such patients can be successfully treated by a combination of CsA and low dose alternate day prednisone therapy. Considering the high relapse rate after stopping CsA and the need for prolonged therapy, in our opinion, steroid dependent patients should first be treated with a course of alkylating agents before resorting to CsA. The results of CsA therapy in steroid resistant idiopathic nephrosis are unsatisfactory. However, CsA in association with prednisone is more effective than CsA alone in inducing remission. Some patients who have entered into complete remission may relapse after the end of the treatment but these relapses may be steroid sensitive. We believe that partial remissions induced by CsA in both steroid sensitive and steroid resistant patients should not be considered as a "success" of therapy as partial remission is most often transient and cessation of therapy is accompanied by an increase of proteinuria. Furthermore, in these patients, prolonged CsA therapy may be harmful.

The main unwanted effect of CsA is chronic nephrotoxicity. CsA should be used with great caution in patients with focal segmental glomerulosclerosis and tubulointerstitial lesions on pre-treatment biopsy. In the absence of response, CsA should not be given for more than four months in order to avoid nephrotoxicity. The lack of correlation between structural damage and renal function indicates that the evaluation of glomerular filtration rate is not a good index to predict the development of irreversible tubulointerstitial lesions. Therefore, repeat renal biopsies should be performed to monitor the effects of prolonged CsA treatment.

REFERENCES


