Cyclosporine in the Treatment of Idiopathic Nephrosis

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ABSTRACT

Within the past decade, there have been numerous reports on the use of cyclosporine in idiopathic nephrosis. In this review, the results of both uncontrolled and controlled studies of the therapeutic effects of cyclosporine in steroid-sensitive/dependent idiopathic nephrosis and in steroid-resistant idiopathic nephrosis are analyzed. Cyclosporine is efficient in up to 80% of patients with steroid-sensitive/dependent idiopathic nephrosis. Most patients, however, relapse when the drug is withdrawn, thus necessitating prolonged treatments. Although cyclosporine is less efficient in patients with steroid-resistant idiopathic nephrosis, a few studies seem to indicate that this drug may be successful in some patients, especially if combined with corticosteroids. There is no evidence that cyclosporine can prevent the recurrence of nephrotic syndrome on the graft after renal transplantation. However, in patients in whom disease has recurred, high doses of cyclosporine may be effective alone or in combination with plasma exchanges. The main worrisome side effect of cyclosporine is chronic nephrotoxicity, which should be differentiated from acute or "functional" toxicity. Follow-up studies including pretreatment and posttreatment renal biopsies show a lack of correlation between structural damage and renal function, suggesting that a histologic examination of the renal parenchyma is the only reliable way of evaluating chronic cyclosporine nephrotoxicity.

Key Words: Cyclosporine, idiopathic nephrosis, renal transplantation, nephrotoxicity, renal biopsy

Cyclosporine has been used in several glomerular diseases that may be associated with nephrotic syndrome, such as systemic lupus erythematosus (1), membranous nephropathy (2–4), immunoglobulin (Ig)A nephropathy (5), and membranoproliferative glomerulonephritis (3). However, the most numerous reports concern idiopathic nephrosis and we will, therefore, focus our review on the results of cyclosporine therapy obtained in this condition.

Idiopathic nephrosis (idiopathic nephrotic syndrome) is defined by the combination of massive proteinuria with nephrotic syndrome and minimal glomerular changes by light microscopy. This "disease," in which the only anomaly is a fusion of foot processes of the podocytes on electron microscopy, is often called minimal change disease (MCD). In some instances, histologic examination may show diffuse mesangial proliferation and/or lesions of focal and segmental glomerular sclerosis (FSGS). In the vast majority of cases, no "deposits" are seen by immunofluorescence (IF) microscopy. If may, however, reveal immunoglobulin mesangial deposits either isolated or in association with C1q and/or C3 deposits. The most frequently found immunoglobulin is IgM (6), but IgA can also be seen (7,8). There have been many retrospective and prospective studies analyzing the clinical significance of these various morphologic features. Many authors use the term idiopathic nephrosis synonymously with MCD; whereas they consider nephrotic syndrome with FSGS, diffuse mesangial proliferation, and/or IgM deposits as distinct "entities." Although morphologic features carry prognostic significance and patients often differ in their response to corticosteroids and in their clinical course, nothing allows at present specific diseases to be identified, and we believe that idiopathic nephrosis should be considered a syndrome with different clinical and histologic variants (9,10).

Clinical experience has shown that the response to steroid therapy carries a greater prognostic weight than the histologic features observed on initial renal biopsy. Therefore, according to the response to corticosteroids, two subtypes of idiopathic nephrosis can be differentiated: a steroid-responsive form and a steroid-resistant form. Up to 85% of patients with idiopathic nephrosis respond to steroid therapy (steroid sensitive), but a high proportion of them relapse when steroid therapy is tapered or soon after the treatment has been stopped (steroid dependent). The risk of developing end-stage renal failure is extremely uncommon in such cases, and the main problems observed are related to complications due to the treatments that are needed to maintain the remission. When the level of steroid therapy required is too high, side effects, mainly growth failure, lead to the use of other drugs such as immunosuppressive agents. The beneficial effects of alkylating agents have been exten-
sively studied in steroid-sensitive patients, but their potential toxic effects limit the duration of treatment (11). After steroid therapy, a small proportion of patients achieve partial remission, with a rise of albuminemia above 30 g/L, although proteinuria is still present. Such patients may also be successfully treated with alkylating agents. Finally, 10 to 15% of the patients fail to respond to steroid therapy. The severity of steroid-resistant idiopathic nephrosis lies both in the extrarenal complications related to the persistence of nephrotic syndrome and in the risk of developing end-stage renal failure. In our experience, after a follow-up of 10 yr, end-stage renal failure occurs in approximately 50% of steroid-resistant patients (10). However, with time, some patients may ultimately achieve partial or even complete remission. There is no clear evidence for the beneficial role of alkylating agents in this situation (12,13), although Mendoza et al. (14) recently reported that an 18-month course of methylprednisolone pulses in association with chlorambucil was effective in a high proportion of steroid-resistant children with FSGS.

The pathophysiology of idiopathic nephrosis is still largely unknown. It has been proposed that activated lymphocytes secrete lymphokines that alter the glomerular basement membrane anionic charges, resulting in proteinuria. The rationale for the use of cyclosporine in patients with idiopathic nephrosis is that this drug suppresses lymphokine production by activated T lymphocytes. It should be kept in mind, however, that cyclosporine also has a nonimmunologic action on the glomerular basement membrane permeability to proteins. Berden et al. (15) studied the effect of cyclosporine in an experimental model of nephritis secondary to antilglomerular basement membrane (GBM) antibodies. They found that the antiproteinuric effect of cyclosporine was the result of a decreased perselectivity of the GBM but not of a decrease of the GFR.

We will review the current experience on the therapeutic effects of cyclosporine in steroid-sensitive idiopathic nephrosis, in steroid-resistant idiopathic nephrosis, and in its recurrence on the graft. We will then discuss the potential side effects of this drug, mainly, nephrotoxicity.

THERAPEUTIC EFFECTS OF CYCLOSPORINE IN IDIOPATHIC NEPHROSIS

The first reports concerning the use of cyclosporine in steroid-sensitive and steroid-dependent idiopathic nephrosis came in 1986 from Hoyer et al. (16) in children and from Meyrier et al. (17) in adults. The authors found that cyclosporine-treated patients had fewer relapses and therefore needed less steroids. Since 1986, there have been a number of uncontrolled studies both in children (18-26) and in adults (27-29) showing that cyclosporine was efficient in 75 to 90% of cases.

In children, only four series involve more than 10 patients each (Table 1). Tejani et al. (20) observed a complete remission in 11 of 13 steroid-dependent children treated with cyclosporine. Four of them had long-lasting remissions after cyclosporine withdrawal. Kitano et al. (21) reported their experience with 17 children with steroid-dependent nephrotic syndrome. No relapse occurred during the 6-month period of cyclosporine treatment, and steroid therapy could be discontinued in all patients. Tanaka et al. (25) treated 19 children with frequent relapses for periods of 18 months. Only two patients relapsed on doses of 3 to 5 mg/kg. Low dose of cyclosporine (2.5 mg/kg) decreased the relapse rate and reduced steroid toxicity. 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 cyclosporine, despite the fact that prednisone had been withdrawn (23). Cyclosporine was ineffective in two patients. The remaining seven patients relapsed after the withdrawal of prednisone treatment, but the association of cyclosporine with low-dose prednisone allowed remission to be maintained. Prolonged cyclosporine 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 Cushie features. Furthermore, in pubertal patients, in whom steroid therapy is particularly deleterious to the pubertal spurt, cyclosporine was of great help (30).

In adults, Lagrue et al. (27) first reported three steroid-dependent patients treated successfully with cyclosporine. Maher et al. (28) reported that cyclosporine had induced a complete remission in 10 of the 11 patients with steroid-responsive nephrotic syndrome. Meyrier and the Collaborative Group of the Société de Néphrologie (29) observed that cyclosporine induced a complete remission in 12 of the 19 patients who had previously responded to corticosteroids.

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**TABLE 1. Results of cyclosporine therapy in steroid-sensitive/dependent idiopathic nephrosis**

<table>
<thead>
<tr>
<th>Group and Reference</th>
<th>No. of Patients</th>
<th>Complete Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capodicasa et al. (18)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Brodehi et al. (19)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Tejani et al. (20)</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Kitano et al. (21)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Melocoton et al. (22)</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Niaudet et al. (23)</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Neuhaus et al. (24)</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Tanaka et al. (25)</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Webb et al. (26)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>129</td>
<td>109 (84.5%)</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lagrue et al. (27)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Maher et al. (28)</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Meyrier et al. (29)</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>33</td>
<td>26 (76%)</td>
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</table>
Pooled data from seven clinical studies, involving both adults and children, were analyzed by the Collaborative Study Group of Sandimmun in Idiopathic Nephrotic Syndrome (31). Adult patients were treated with a mean daily dose of 4.8 ± 1.8 mg/kg body wt, and children were treated with a mean daily dose of 5.6 ± 1.6 mg/kg body wt. Among the 104 steroid-dependent patients, 80% achieved complete remission and 8% achieved partial remission, whereas 12% failed to respond to cyclosporine. In the patients who responded to cyclosporine, remission occurred rapidly, usually during the first month of treatment.

Most patients, in the published series, experienced relapses of the nephrotic syndrome when the dose of cyclosporine was tapered or when the drug was withdrawn. The patients thus behave with cyclosporine in the same way they used to behave with steroids, i.e., they become cyclosporine dependent. The relapse rate usually returns to the pretreatment frequency. Hultin et al. (32) found that patients in whom cyclosporine had been discontinued and then restarted later had more relapses, requiring steroids in addition to cyclosporine in order to maintain remission. In our experience, also, the treatment has often been less effective during subsequent treatment courses in children who were restarted on cyclosporine after the discontinuation of the drug. Such patients were successfully treated by a combination of cyclosporine and low-dose, alternate-day prednisone therapy (23).

The therapeutic effects of cyclosporine have also been evaluated in two comparative trials in patients with steroid-sensitive idiopathic nephrosis. The French Society of Pediatric Nephrology compared cyclosporine at the dose of 6 mg/kg body wt per day for 3 months, then tapered over 3 months, with chlorambucil given for 2 months to a total nongonadotoxic dose of 8 mg/kg body wt in children with steroid-dependent idiopathic nephrosis (33). Twenty patients 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 cyclosporine were still in remission. A multicenter randomized control trial was performed in Italy comparing cyclosporine for 9 months, then tapered over 3 months, with oral cyclophosphamide for 2 months (34). This trial involved 55 children and 11 adults with steroid-dependent and frequently relapsing nephrotic syndrome. The relapse rate and the mean steroid dose during the treatment period were comparable in both groups. At 2 yr, 25% of the patients (50% of adults and 20% of children) who had received cyclosporine had not relapsed, whereas 63% of those treated with cyclophosphamide (40% of adults and 68% of children) were still in remission. During the year after the treatment, the relapse rate (1.8 versus 0.7) and the dose of steroid required (109 versus 23 mg/kg per year) were significantly higher in the children who had received cyclosporine (35).

Only one group has used cyclosporine as the first-line treatment of nephrotic syndrome in children. Tejani et al. (36) performed a randomized, controlled trial comparing low-dose prednisone associated with cyclosporine with high-dose prednisone for 8 wk in 28 children with nephrotic syndrome. Thirteen of the 14 children receiving the combined treatment went into remission compared with only 8 of the 14 children receiving prednisone alone (P < 0.05). The main difference was that patients with FSGS responded better to the combined treatment (three out of four) than did those treated with prednisone alone (one out of five). The duration of remission after the discontinuation of therapy was comparable in both groups.

Ingulli and Tejani (37) recently reported that severe hypercholesterolemia may inhibit cyclosporine efficacy. Among 47 children who received cyclosporine at a dose of 6 mg/kg body wt for 2 months, 13 failed to respond. These patients had a higher serum cholesterol level than did the ones who responded, and this feature was the only significant predictor of cyclosporine responsiveness. Seven of the 13 nonresponders were retreated with higher doses of cyclosporine (10 to 14 mg/kg body wt), and 5 of them responded to the treatment without evidence of nephrotoxicity.

Contrasting with its beneficial effect in steroid-sensitive patients, cyclosporine 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 (18–20,22,23,38–40) (Table 2). Similar results have been reported in four series of adults involving 49 patients, of whom 6 achieved complete remission (27–29,41). The Collaborative Study Group of Sandimmun in Nephrotic Syndrome analyzed the pooled data from seven clinical studies (31). Of the 226 steroid-resistant patients, 19%...
achieved complete remission and 18% achieved partial remission. The rate of complete and partial remissions was significantly higher when cyclosporine was administered in combination with prednisone. Complete remission occurred in 24% of patients treated with cyclosporine combined with low-dose prednisone and in 14% of patients receiving cyclosporine alone.

The French Society of Pediatric Nephrology performed a prospective trial involving 65 children who received cyclosporine (150 to 200 mg/m² per day) in combination with low-dose prednisone (30 mg/m² per day) for 1 month and the same dose on alternate days, thereafter, for 5 months. Preliminary results of that study have been reported earlier (42). Forty-two percent of them went into complete remission and 6% went into 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. In a few patients, the remission occurred much later, between the fourth and the sixth months. Interestingly, eight patients who relapsed after cyclosporine treatment responded further to prednisone and experienced a steroid-dependent course. Nine patients had not relapsed 13 to 35 months after cyclosporine withdrawal. Furthermore, at latest follow-up, only two patients had a persistent nephrotic syndrome and all patients had a normal GFR. The rapidity of the response after the 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. 1 of them after having received a course of alkylating agents and the other 4 while receiving only supportive therapy. At latest examination, 2 patients were in partial remission and 10 had a persistent nephrotic syndrome, associated with moderate renal insufficiency in 5. Twelve unresponsive patients progressed to terminal renal failure. The main question concerns the role of cyclosporine in this progression. Cyclosporine is likely to be partly responsible for this evolution in one patient who was started on hemodialysis 4 months after the initiation of therapy. However, the rate of progression to renal failure in the remaining patients was similar to that of a series of patients from the Necker-Enfants Malades Hospital who had not received cyclosporine (10). Last, four patients achieved partial remission that was transient and cessation of therapy was accompanied by an increase in proteinuria.

The effect of cyclosporine has also been studied in two comparative trials in patients with steroid-resistant idiopathic nephrosis. Ponticelli et al. (43) conducted a randomized trial comparing cyclosporine alone with supportive therapy. Cyclosporine was given at full dose for 6 months and reduced by 25% every 2 months thereafter. Among the 22 patients (12 adults and 10 children) who received cyclosporine, 7 entered into complete remission, 6 entered into partial remission, and 9 did not respond to the treatment. Conversely, in the control group, 3 of the 19 patients achieved partial remission and none went into complete remission. Only 38% of the patients who responded to cyclosporine were still in remission at 1 yr. Tejani and Lieberman (44) recently reported the results of a randomized trial comparing cyclosporine at a dose of 6 mg/kg per day for 6 months with placebo in steroid-resistant FSGS in children. Complete remission was observed in 4 of the 11 patients receiving cyclosporine compared with none of the 11 patients receiving placebo. Partial remission was obtained in seven patients on cyclosporine and in two patients receiving placebo.

It is of interest that the response to cyclosporine of patients with idiopathic nephrosis is better correlated with the initial steroid responsiveness than with the histopathologic categories. We previously showed that 64% of the patients with MCD or diffuse mesangial proliferation and 66% of the patients with FSGS responded to cyclosporine, whereas 85% of the steroid-dependent patients and only 10% of the steroid-resistant patients responded to the drug (45). The pooled data from seven uncontrolled studies showed that the rate of remission was 60% in patients with MCD and 20% in patients with FSGS, whereas 80% of the steroid-dependent and 19% of the steroid-resistant achieved complete remission (31).

RECURRENT OF THE NEPHROTIC SYNDROME IN RENAL TRANSPLANT PATIENTS

The major problem of patients with idiopathic nephrosis who progress to end-stage renal failure and who undergo renal transplantation is the risk of recurrence of the nephrotic syndrome. The overall risk of recurrence is estimated to be around 30% (46). The risk is higher in children than in adult patients. In children, recurrence is more frequent when the onset of the original disease occurs after the age of 6 yr than before that age. A rapid progression of the disease to end-stage renal failure seems also to be a major risk factor. In addition, recurrence occurs more frequently in patients in whom the initial biopsy performed during the course of the original disease showed diffuse mesangial proliferation (47). Graft failure occurs in about 60% of patients with recurrence, but some patients may show good renal function for several years despite persistent nephrotic syndrome.

There is no evidence that cyclosporine can prevent the recurrence of nephrotic syndrome after transplantation. Aztero et al. (48) found no difference in the rate of recurrence on the graft in patients receiving cyclosporine compared with patients receiving conventional therapy. Similarly, Banfi et al. (49) found no effect of cyclosporine in these patients. Recurrence of the nephrotic syndrome was observed in 2 of the 6 patients receiving azathioprine compared with 10 of the 19 patients who were given cyclosporine.

In patients in whom disease has recurred, high
doses of cyclosporine may be effective. Mowry et al. (50) recently reported on 11 children who received 12 renal transplants and who had developed severe recurrent nephrotic syndrome after renal transplantation. Nine patients received high doses of cyclosporine, eight were treated with 10 to 12 plasma exchanges, and six were treated with a combination of plasma exchanges and high doses of cyclosporine. Remission was observed in 10 of the 12 recipients. The optimal timing for performing plasma exchanges or for increasing the dose of cyclosporine has still to be determined. Ingulli and Tejani (51) reported two children with recurrent nephrotic syndrome while on cyclosporine and prednisone. They both achieved remission when the dose of cyclosporine was gradually increased from 15 to 27 and 35 mg/kg per day.

**SIDE EFFECTS OF CYCLOSPORINE THERAPY**

The main unwanted effect of cyclosporine is nephrotoxicity. Acute nephrotoxicity, which is related to a reduced RBF, should be differentiated from chronic nephrotoxicity. This so-called functional toxicity does not usually lead to permanent kidney damage. In patients with steroid-dependent idiopathic nephrosis receiving cyclosporine, a transient renal insufficiency often occurs during a relapse. Tirelli et al. (52) studied the renal effects of cyclosporine in eight children with steroid-dependent idiopathic nephrosis. Compared with children receiving only steroids, those treated with cyclosporine showed a decrease in the GFR with an increased reabsorption activity of proximal tubular cells, as demonstrated by a decreased fractional excretion of β2-microglobulin and uric acid. It is now well established that cyclosporine causes a vasoconstriction of the afferent arterioles and several mechanisms are involved in this process: effect on smooth muscle cells, release of prostaglandin derivatives and platelet-activating factor from endothelial cells, release of endothelin and of renin (53,54). These effects are responsible for a decrease in GFR with a concomitant rise in serum urea and creatinine that is dose dependent and usually reversible when the dose of cyclosporine is reduced or when the drug is stopped.

We have seen that cyclosporine is efficient in most patients with steroid-sensitive/dependent nephrotic syndrome, but these patients relapse after cyclosporine tapering or withdrawal, thus necessitating prolonged therapy. However, several reports indicate that the protracted use of cyclosporine may be associated with chronic renal injury, even in patients with normal renal function, suggesting that the only reliable way of evaluating chronic cyclosporine nephrotoxicity is to investigate the structural damage of the renal parenchyma. Morphologic renal changes induced by cyclosporine were first reported in kidney transplant patients (55,56). These changes are now much better defined because they have been observed in patients with previously healthy kidneys such as cardiac transplant patients (57–60) or patients with autoimmune diseases (61–68). Two features are highly suggestive of chronic nephrotoxicity. The first one is the so-called cyclosporine-associated arteriolopathy, which has been considered to be specific and is characterized by the presence in the arterial wall of circular nodular deposits in place of necrotic smooth muscle cells (56). The second one is the presence of tubulointerstitial lesions, characterized by a combination of stripes of interstitial fibrosis always containing atrophic tubules. In recent articles and probably because the doses of cyclosporine have been diminished, the so-called cyclosporine-associated arteriolopathy is rarely found, and it seems well established that the most prominent changes suggesting nephrotoxicity, although unspecific, are the development of tubulointerstitial lesions.

In order to evaluate chronic nephrotoxicity, we compared posttreatment renal biopsies with pretreatment biopsies in a group of 42 patients with idiopathic nephrosis who had received cyclosporine for periods ranging from 4 to 63 months (69). A similar study had been performed in 1988 by Classen et al. (70), who reported five patients who had been treated with cyclosporine for a mean period of 10 months. None of the five patients showed significant vascular or interstitial lesions on posttreatment biopsies. In our study, the evaluation of nephrotoxicity was based on the severity of tubulointerstitial lesions rather than on the presence of arteriolar lesions because 10 of the 42 patients examined showed unspecific arteriolar lesions characterized by subendothelial widening with or without hyaline deposits, but none showed the so-called cyclosporine-associated arteriolopathy. In order to establish correlations with the dose and duration of cyclosporine and with renal function, we arbitrarily graded the tubulointerstitial changes into three 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 was assigned when confluent or extensive areas of interstitial fibrosis with atrophic and/or collapsed tubules were observed. The overall results of the posttreatment biopsies showed no or minor tubulointerstitial lesions in 18 patients (Grade I), several foci of atrophic tubules (Grade II) in 15 patients, and more extensive tubulointerstitial lesions (Grade III) in 9 patients.

The interpretation of tubular and interstitial lesions in patients with idiopathic nephrosis is hazardous because one cannot exclude with certainty that the changes observed are not related to the possible progression of the disease itself, particularly if lesions of FSGS are present. In our study, of the 11 patients with FSGS on posttreatment biopsies, tubular atrophy and interstitial fibrosis of Grade II were observed in 6 patients. Excluding these 6 patients, it remains that 9
of the 15 children who developed Grade II tubulointerstitial damage had MCD on both pretreatment and posttreatment biopsies, suggesting that the lesions observed are possibly related to cyclosporine. More interesting, none of the nine patients who showed Grade III tubulointerstitial lesions in the latest biopsy specimen obtained either had FSGS on pretreatment biopsy or developed FSGS on subsequent biopsies. We interpreted these rather severe tubulointerstitial changes with normal or nearly normal glomeruli as indicative of cyclosporine nephrotoxicity.

It has been suggested that the development of cyclosporine-associated chronic nephropathy is dose dependent (67). Therefore, the starting dose of cyclosporine should not exceed 5 mg/kg body wt per day in adults and 150 mg/m^2 per day in children. The importance of measuring cyclosporine blood levels during the treatment remains a controversial issue. In our experience, there was no correlation between the severity of tubulointerstitial lesions and either the mean cyclosporine dose administered or the trough cyclosporine blood levels. Although the severity of tubulointerstitial damage was not correlated with the duration of cyclosporine therapy, our study showed that tubulointerstitial lesions may increase with time. This was clearly demonstrated on serial biopsies from four patients with kidneys within normal limits on the first posttreatment biopsy and who developed Grade III tubulointerstitial lesions after 25 to 63 months of cyclosporine. Furthermore, two of the three patients with moderate tubulointerstitial lesions on the first posttreatment biopsy (Grade II) developed severe tubulointerstitial lesions on the latest biopsy obtained after, respectively, 29 and 32 months of cyclosporine therapy. On latest evaluation, all of our patients had normal GFR, including the nine patients with Grade III tubulointerstitial lesions. The lack of correlations between more or less severe structural damage and renal function indicates that the evaluation of GFR is, therefore, not a reliable index with which to predict the development of chronic cyclosporine nephrotoxicity.

Hypertension develops in 14% of patients with idiopathic nephrosis treated with cyclosporine, and its incidence is similar in adults and in children. Hypertension is more frequent in steroid-resistant patients (18%) than in steroid-dependent patients (5%) (71). Malignant tumors have been reported in three patients (71). Two patients had Hodgkin’s lymphoma, and one had bronchial carcinoma. Patients had received cyclosporine for 3 to 22 months when the tumor was diagnosed.

The other well-known side effects include hypertrichosis, gum hyperplasia, gastrointestinal disturbances, paresthesia, tremor, or headache. Hyperkalemia may be observed, particularly when the GFR is decreased. A decrease of serum magnesium may be noted.

CONCLUSIONS

Cyclosporine 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 cyclosporine is tapered or when the treatment is withdrawn. Cyclosporine is often less effective when the treatment has been discontinued and restarted later. Such patients can be successfully treated by a combination of cyclosporine and low-dose, alternate-day prednisone therapy. Considering the high relapse rate after cyclosporine is stopped 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 cyclosporine. The results of cyclosporine therapy in steroid-resistant idiopathic nephrosis are poor. However, cyclosporine in association with prednisolone is more effective than cyclosporine 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 cyclosporine in both steroid-sensitive and steroid-resistant patients should not be considered a “success” of therapy because partial remission is most often transient and cessation of therapy is accompanied by an increase of proteinuria. Furthermore, in these patients, prolonged cyclosporine therapy may be harmful. The main unwanted effect of cyclosporine is chronic nephrotoxicity. Cyclosporine should be used with great caution in patients with FSGS and tubulointerstitial lesions on pretreatment biopsy. In the absence of response, cyclosporine should not be given for more than 4 months in order to avoid nephrotoxicity. The lack of correlation between structural damage and renal function indicates that the evaluation of GFR is not a good index with which to predict the development of irreversible tubulointerstitial lesions. Therefore, repeat renal biopsies should be performed to monitor the effects of prolonged cyclosporine treatment.

REFERENCES


