Editorial Review

Cyclosporine (CsA) in lupus nephritis: assessing the evidence

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Introduction

After more than 40 years since the first demonstration that high-dose corticosteroids can modify the relentless outcome of lupus nephritis [1], the ideal treatment of lupus nephritis is still far from being established. There is some agreement that the initial treatment should be aggressive, particularly in proliferative forms (so-called induction therapy) and should be followed by a maintenance regimen aimed at preventing flares of activity while minimizing the side effects of treatment. However, there are differing views on how to use the available immunomodulating drugs in the various phases of the disease. In particular, there is still much controversy about the current therapies for maintenance [2]. Notwithstanding the different approaches used, it should be noted that the treatment of systemic lupus erythematosus (SLE) nephritis relies on three main categories of drugs, i.e. corticosteroids, alkylating agents and inhibitors of purine synthesis. However, all these drugs have a narrow therapeutic index, and their prolonged administration can cause severe iatrogenic toxicity. In this review, we will try to assess whether cyclosporine (CsA), a drug that interferes with the immune response at levels different from those of corticosteroids and immunosuppressive drugs, may have a role to play in the therapeutic armamentarium of lupus nephritis.

CsA is a pro-drug that gains pharmacological activity after binding to its specific cytoplasmic receptor cyclophilin. The complex CsA–cyclophilin interferes with a complex of phosphatases called calcineurin that has a key role in the immune response. Contact with the antigen-presenting cell generates a strong influx of calcium ions into the lymphocytes, which results in activation of calcineurin with consequent dephosphorylation of a family of proteins called nuclear factor activating T cells (NFAT). After being dephosphorylated by calcineurin, NFAT enters the nucleus where it participates in the synthesis of interleukin-2 that triggers lymphocyte proliferation. Thus CsA may disrupt progression of the activated cascade by dampening T-cell production of pro-inflammatory cytokines and arresting the cell cycle between G0 and G1. This mechanism of action makes CsA an attractive drug for autoimmune diseases. The pro-inflammatory cytokines interplay among the cellular, immunological and biochemical mediators of inflammation at multiple levels; they, not only exert a critical role in the initiation and propagation of autoimmune disorders, such as SLE, but can also facilitate the migration of lymphocytes to specific target organs, thus accounting for the accumulation of T cells in different organs, including the kidney. In turn, T-autoreactive T-cell clones provide the first amplification loop after the antigen presentation, maintain the inflammation and predispose to organ damage. Interrupting the T-cell amplification loop can lead to maintenance of the whole process under the autoimmune threshold [3].

However, CsA can exert untoward events including arterial hypertension, hyperlipaemia, diabetes, which may worsen the cardiovascular profile in lupus patients, and nephrotoxicity. These side effects are usually dose related. Therefore, it may be dangerous to use high doses of CsA as a therapy of induction in lupus nephritis. The drug might better be suited for maintenance therapy, particularly in patients with moderate-severe proteinuria and in those patients in whom it is desirable to diminish the doses of corticosteroids and immunosuppressive agents. In addition, CsA can be used as a second-line induction therapy in patients with active lupus nephritis unresponsive to conventional therapy.

Use of CsA in SLE

There are two formulations of CsA. The original formulation (Sandimmune; Novartis, Basel, Switzerland), now also available as a generic drug, has a poor bioavailability and large inter- and intra-subject pharmacokinetic
variability, while a new microemulsion (Neoral; Novartis), available since 1990, has a better bioavailability and a more predictable pharmacokinetics and dose linearity.

The first experience with the original CsA in SLE patients was carried out by Isenberg et al. in 1981 [4]. CsA was given to five patients with active SLE at a dose of 10 mg/kg/day orally. It was not possible for any patient to take the drug for longer than 7 weeks because of side effects including nephrotoxicity. Two patients experienced an improvement in their arthralgias, but given the side effects induced, the authors did not recommend CsA for the treatment of SLE. In more recent years, however, the better knowledge of the drug and of its effects made it possible to reduce the doses of CsA both in autoimmune diseases and in kidney transplantation, with a proportional reduction of side effects. In SLE, good results were obtained with initial doses of CsA ranging between 3 and 5 mg/kg/day [5–8].

In the columns 'Proteinuria' and 'Renal function', the first data refer to the baseline and the last ones to the results observed at the last follow-up visit. CsA: cyclosporine; GFR: glomerular filtration rate.

### Treatment of lupus nephritis with CsA

#### Proliferative lupus nephritis

In 1989, Favre et al. [9] administered CsA (5 mg/kg/day) to 18 patients with class III or IV lupus nephritis who did not respond to conventional therapy. Patients were followed for 24–52 months; proteinuria went below 1 g/day in all patients, renal function improved in some patients and it was possible to reduce steroids markedly. Following this experience, a few other case series [10–16] reported improvement in proteinuria and stable renal function with CsA in patients with proliferative lupus nephritis who had shown poor or no response to previous immunosuppressive therapies (Table 1). In most patients it was possible to lower the maintenance doses of corticosteroids. In some studies [13,15], the titres of anti-DNA antibodies decreased and the serum levels of C3 or C4 increased, while other investigators [14,16] did not find significant variations of anti-DNA antibodies and serum levels of complement. Taken together, these studies provided only levels of evidence 5–6 according to the criteria proposed by Carruthers et al. [17].

Two randomized, controlled trials providing levels of evidence 1–2 are also available (Table 2). In 1998, Fu et al. [18] performed an open randomized study on 40 children with class III or IV lupus nephritis and persistent nephrotic proteinuria notwithstanding intravenous methylprednisolone pulses (MPP) and oral prednisolone being administered for 1 year or more. Patients were assigned to receive either CsA Neoral alone (5 mg/kg/day) or prednisolone (2 mg/kg/day) plus oral cyclophosphamide (2 mg/kg/day) for 1 year. Proteinuria significantly decreased to a non-nephrotic range in both groups. A slight, non-significant decline in creatinine clearance was observed in the CsA group. Serum C3 and CH50 decreased in the CsA group, while anti-DNA antibodies titres decreased in both groups, although more markedly in the prednisolone–cyclophosphamide group. The most important result was a significant improvement in growth velocity in children given CsA alone, in comparison to no change in children assigned to prednisone and cyclophosphamide.

An Italian group of nephrologists and rheumatologists carried out a multicentre randomized controlled trial in adults with diffuse proliferative lupus nephritis [19] to compare the efficacy and safety of CsA and azathioprine. After an induction therapy of 3 months with three intravenous MPP followed by prednisone at a mean daily dose of 39 ± 11 mg and oral cyclophosphamide at a mean daily dose of 91 ± 24 mg, 75 patients with biopsy-proven class IV lupus nephritis were randomized to receive prednisone in tapering doses (mean 6 mg/day at 4 years) and Neoral at a mean starting dose of 3.5 ± 0.5 mg/kg/day followed by a maintenance dosage of 2.1 ± 0.97 mg/kg/day, or azathioprine at a mean starting dose of 1.6 ± 0.5 mg/kg/day followed by a maintenance dosage of 0.9 ± 0.35 mg/kg/day. Treatment continued for up to 4 years. The primary end point was the incidence of lupus flares: seven occurred in the CsA group and eight in the azathioprine group. At the end of the follow-up, mean proteinuria significantly decreased

### Table 1. Impact of cyclosporine treatment on proteinuria and renal function in patients with proliferative lupus nephritis

<table>
<thead>
<tr>
<th>Authors and level of evidence</th>
<th>Patients</th>
<th>CsA (mg/kg/day)</th>
<th>Follow-up (months)</th>
<th>Proteinuria</th>
<th>Renal function</th>
<th>Repeat renal biopsy patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favre [9] Level 5</td>
<td>26 (18)</td>
<td>5</td>
<td>52</td>
<td>From nephrotic syndrome to &lt; 1 g/day</td>
<td>Improved in seven patients</td>
<td>26</td>
</tr>
<tr>
<td>Hussein [10] Level 6</td>
<td>5 (4)</td>
<td>2–4</td>
<td>18</td>
<td>From 3.6 ± 2.1 to 0.08 ± 0.18 g/day</td>
<td>Serum creatinine from 0.8 ± 0.12 to 0.83 ± 0.18 mg/dl</td>
<td>None</td>
</tr>
<tr>
<td>Dostal [13] Level 5</td>
<td>11 (9)</td>
<td>3.5</td>
<td>12</td>
<td>From 9.1 ± 4.2 to 1.45 ± 1.27 g/day</td>
<td>GFR from 1.26 ± 0.5 to 1.19 ± 0.44 ml/s</td>
<td>8</td>
</tr>
<tr>
<td>Tam [14] Level 5</td>
<td>17 (17)</td>
<td>5–2.5</td>
<td>43</td>
<td>From 5.6 ± 2.5 to 0.7 ± 0.6 g/day 24 h</td>
<td>GFR from 73.1 ± 29.6 to 74.3 ± 31.5 ml/min</td>
<td>17</td>
</tr>
<tr>
<td>Rihova [15] Level 5</td>
<td>24 (24)</td>
<td>5</td>
<td>89</td>
<td>From 3.17 g/day 24 h (range 1–12) to 0.4 g/day 24 h (range 0–0.8)</td>
<td>GFR from 1.54 ± 0.38 to 1.38 ± 0.3 ml/s</td>
<td>13</td>
</tr>
</tbody>
</table>

All studies were retrospective. The level of evidence has been evaluated according to the criteria of Carruthers et al. [17]. In the column of patients, the numbers of patients with proliferative nephritids are indicated in parentheses.
Cyclosporine (CsA) in lupus nephritis

Table 2. Randomized controlled trials with cyclosporine therapy

<table>
<thead>
<tr>
<th>Authors and level of evidence</th>
<th>Treatment and number of patients</th>
<th>Doses (mg/kg/day)</th>
<th>Follow-up (months)</th>
<th>Proteinuria (from baseline to the last visit)</th>
<th>Creatinine clearance (from baseline to the last visit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu [18] Level 2</td>
<td>CsA 20</td>
<td>3.5–5</td>
<td>12</td>
<td>From 4.62 ± 1.93 to 0.35 ± 0.28 g/day</td>
<td>From 122.4 ± 19.4 to 104.6 ± 16.8 ml/min</td>
</tr>
<tr>
<td>Moroni [19] Level 1</td>
<td>CsA + Prednisone 20</td>
<td>2 ± 2</td>
<td>12</td>
<td>From 4.5 ± 1.86 to 0.62 ± 0.2 g/day</td>
<td>From 128.5 ± 6.7 to 120.3 ± 4.5 ml/min</td>
</tr>
<tr>
<td>Rashakrishan [24] Level 5</td>
<td>CsA 10</td>
<td>4</td>
<td>12</td>
<td>From 2.8 ± 3.6 to 0.23 ± 0.24 g/day</td>
<td>From 92.5 ± 21.5 to 80 ± 15 ml/min</td>
</tr>
<tr>
<td>Tam [26] Level 5</td>
<td>Cyclosporine 36</td>
<td>4 ± 0.5</td>
<td>48</td>
<td>From 2.2 ± 1.94 to 0.33 ± 0.33 g/day</td>
<td>From 104.1 ± 46.5 to 104 ± 40.1 mg/dl</td>
</tr>
</tbody>
</table>

The level of evidence has been evaluated according to the criteria of Carruthers et al. [17].

Table 3. Results of retrospective studies with cyclosporine in membranous lupus nephritis

<table>
<thead>
<tr>
<th>Authors and level of evidence</th>
<th>Patients</th>
<th>CsA (mg/kg/day)</th>
<th>Follow-up (months)</th>
<th>Proteinuria (g/day; baseline and last visit)</th>
<th>Response (proteinuria &lt; 1 g/day)</th>
<th>Serum creatinine (mg/dl; baseline and last visit)</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rashakrishan [24] Level 5</td>
<td>10</td>
<td>4</td>
<td>30</td>
<td>5.8–1.1</td>
<td>10/10</td>
<td>0.8–0.95</td>
<td>3/10</td>
</tr>
<tr>
<td>Hallegue [23] Level 5</td>
<td>10</td>
<td>3.8</td>
<td>24</td>
<td>5.5–1.4</td>
<td>9/10</td>
<td>1.1–1.25</td>
<td>2/9</td>
</tr>
<tr>
<td>Tam [26] Level 5</td>
<td>10</td>
<td>5–2.5 + AZA 1 mg/kg/day</td>
<td>36</td>
<td>5.6–0.8 in responders</td>
<td>7/10</td>
<td>GFR 81–106</td>
<td>4/7</td>
</tr>
<tr>
<td>Hu [27] Level 5</td>
<td>23</td>
<td>4.7</td>
<td>17</td>
<td>5.1–0.3</td>
<td>22/23</td>
<td>0.86–0.95</td>
<td>4/23</td>
</tr>
</tbody>
</table>

The level of evidence has been evaluated according to the criteria of Carruthers et al. [17]. In the columns ‘Proteinuria’ and ‘Serum creatinine’, the first data refer to baseline results and the second data to the results at the last follow-up visit.

Membranous lupus nephritis (Table 3)

Current data indicate that CsA is effective in inducing a partial or complete remission of proteinuria in between 60 and 75% of cases of idiopathic membranous nephropathy [23]. In view of the histological and clinical similarity with idiopathic membranous nephropathy, it would be reasonable to expect similar results also in SLE pure membranous nephropathy. Four small-sized retrospective studies [24–27] reported the results of CsA therapy in lupus patients with membranous nephritis (MN). Patients were followed for 17–36 months. The mean initial doses of CsA ranged around 2–5 mg/kg/day with a small reduction in some cases. About 90% responded to treatment with a complete or partial remission. The mean proteinuria decreased during treatment from 5–6 g/day to 0.3–1.4 g/day. A mild increase in serum creatinine was observed in three studies [24,25,27] while in another paper the mean levels of glomerular filtration rate increased during CsA treatment [26]. Relapse of proteinuria occurred in a number of patients after interruption of CsA. Treatment was generally well tolerated.
Adverse events

The studies that used CsA at low doses reported that CsA was well tolerated [11,13–16,19,24,26,27]. A mild non-progressive increase in serum creatinine was observed in most patients, but it returned to basal values after CsA was withdrawn. Arterial hypertension was frequently reported (in 10–60% of cases) but was generally easy to control with antihypertensive therapy. Other frequent side effects were gingival hyperplasia (5–30%), hypertrichosis (6–60%) and hyperuricaemia (40–60%).

Repeat renal biopsies

In our study [19], we repeated renal biopsy in 14 patients of the CsA group and 15 of the azathioprine group after 2 years of therapy. The activity index significantly decreased and the chronicity index slightly increased in both groups, without any difference between CsA and azathioprine. Some other studies [13,14,24,29] have also reported the results of repeat renal biopsies at the end of treatment with CsA (Table 4). According to the clinical results, the activity index decreased in all studies, while there was a mild, non-significant, increase in chronicity index, and no cases of severe CsA-related renal toxicity were reported.

Conclusions

The choice of maintenance treatment for patients with lupus nephritis remains a major challenge. To prevent the disease-related complications, treatments with corticosteroids and/or immunosuppressive drugs are generally adopted; however, the prolonged use of these drugs can be loaded with severe and even life-threatening complications. Therefore, any drug that is able to restrain the activity of SLE with the lowest possible use of corticosteroids and/or immunosuppressive agents is welcome. The above-reported studies showed that CsA may replace cytotoxic drugs and diminish the dosage of corticosteroids for maintenance treatment. Limitations of these studies are represented by the small number of patients investigated, relatively short-term follow-ups and paucity of randomized controlled trials. However, a review of the few available studies showed that CsA was efficacious in quenching the clinical and histological manifestation of lupus nephritis even in patients who did not respond to previous immunosuppressive therapy. In particular, CsA proved to be effective in reducing proteinuria both in proliferative and membranous nephritis, avoiding the renal and extra-renal risks of a protracted nephrotic syndrome.

Low-dose CsA may also make it possible to replace other immunosuppressive drugs and to decrease the doses of prednisone, reducing the risks of invalidating and life-threatening complications. As showed by Fu et al. [18], the possibility of avoiding or minimizing corticosteroids could be of particular benefit to children and adolescents by restoring somatic growth and improving adherence to prescribed therapies. However, the serological activity of lupus does not burn out in all patients. This dissociation between clinical and serological activity is not completely unexpected since CsA mainly inhibits pro-inflammatory cytokines and T helper activity, while it has little impact on humoral immunity. On the other hand, it is well known that, with the possible exception of anti-C1q antibodies, a discrepancy between clinical and serological activity is not infrequent in patients with SLE [30]. Whether the lack of serological remission could represent a potential for disease reactivation is still a matter of debate. Some studies

Table 4. Modifications of the activity and chronicity indices at repeat renal biopsy after cyclosporine treatment

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Basal RB Ac. index</th>
<th>Second RB Ac. index</th>
<th>P</th>
<th>Basal RB Cr. index</th>
<th>Second RB Cr. index</th>
<th>P</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radhakrishnan [24]</td>
<td>5</td>
<td>4 (1–9)</td>
<td>1.6 (1–3)</td>
<td>ns</td>
<td>2.6 (0–7)</td>
<td>3.8 (2–6)</td>
<td>ns</td>
<td>10</td>
</tr>
<tr>
<td>Liu [29]</td>
<td>16</td>
<td>7.2</td>
<td>2.9</td>
<td>NA</td>
<td>5.1</td>
<td>5.7</td>
<td>NA</td>
<td>12</td>
</tr>
<tr>
<td>Dostal [13]</td>
<td>8</td>
<td>7.7 ± 4.1</td>
<td>2.1 ± 1.3</td>
<td>&lt;0.02</td>
<td>3.1 ± 3.1</td>
<td>3.6 ± 2.3</td>
<td>ns</td>
<td>12</td>
</tr>
<tr>
<td>Tam [14]</td>
<td>17</td>
<td>10.1 ± 4.7</td>
<td>4.9 ± 1.8</td>
<td>&lt;0.001</td>
<td>5.1 ± 0.5</td>
<td>5.7 ± 0.6</td>
<td>ns</td>
<td>12</td>
</tr>
<tr>
<td>Moroni [19]</td>
<td>14</td>
<td>5.9 ± 3.9</td>
<td>1.4 ± 3.2</td>
<td>&lt;0.003</td>
<td>2.3 ± 1.5</td>
<td>3.7 ± 1.8</td>
<td>ns</td>
<td>24</td>
</tr>
</tbody>
</table>

In the paper of Radhakrishnan et al. [24], all patients had a lupus membranous nephropathy, while in the other papers all patients had a proliferative lupus nephritis.

RB: renal biopsy; Ac. index: activity index; Cr. index: chronicity index; NA: not available; ns: non-significant.
[14,24] have reported renal and/or extra-renal reactivations of SLE after withdrawal of CsA. Nevertheless, it has been shown that protracted clinical quiescence can be maintained without therapy adjustments in spite of persistent immunological activity [31].

Although the studies describing repeat renal biopsy have shown neither a significant increase in chronicity index nor signs of CsA nephrotoxicity, the most worrying drawback of CsA therapy remains its potential chronic nephrotoxicity. To avoid this risk, we recommend that CsA should not be used in lupus patients with creatinine clearance \(<60\) ml/min, and/or in patients with severe interstitial fibrosis at renal biopsy. Hypertensive patients should be treated with CsA only if arterial hypertension is well controlled by anti-hypertensive therapy. The initial doses of CsA should not exceed 5 mg/kg/day. In cases of good response, the doses should be slowly and cautiously tapered to 2–3 mg/kg/day as a maintenance therapy to avoid the risks of fulminant flares that have been reported in two cases after the abrupt discontinuation of CsA [32]. In a few cases, proteinuria may be maintained below 1 g/day even with minimal doses of CsA, i.e. 1.5–2.0 mg/kg/day. Serum creatinine should be monitored every 2 weeks in the first 2 months, monthly for the first 6 months and then at least every 2 months. Increases of serum creatinine up to 20\% over the baseline generally do not need any modification of the dosage. However, the dose should be reduced by 25\% if serum creatinine increases \(\geq 30\%\) above the baseline. CsA should be further reduced by another 25\% if serum creatinine does not improve after the first reduction. For increases in serum creatinine over 50\%, it is advisable to halve the initial doses and to stop CsA if there is no response after 2–4 weeks. The drug should also be stopped whenever the increase in serum creatinine is \(\geq 75\%\) over the basal value [33].

In some instances, it may be difficult to attribute an increase in serum creatinine to the progression of nephritis or to CsA nephrotoxicity. Usually (but not always!) a flare of lupus is associated with an increase in anti-C1q and anti-DNA antibodies and with a decrease in serum complement. From a clinical point of view, extra-renal signs and symptoms of SLE activity are frequent; the increase in serum creatinine is usually rapid and associated with proteinuria and an active sediment, while in the case of CsA toxicity, the increase in serum creatinine is slower and almost asymptomatic. In difficult cases, a renal biopsy may help. However, in cases of silent progression leading to chronic lesions, the absence of histological signs of SLE activity does not exclude a progression of nephritis. In these cases, however, whatever the cause, we suggest to stop the use of CsA.

A further measure to improve the tolerance of the drug and the compliance of the patient is a single-day administration. Both in organ transplant recipients [34] and in patients with idiopathic nephrotic syndrome [35–37] there are reports that show that giving the daily dose of CsA in a single-morning administration is as effective as an administration every 12 h, but with fewer side effects. We are now using such a strategy in patients with lupus nephritis.

A still unanswered question is how long CsA can be safely administered to lupus patients. Responders with stable renal function receiving daily doses of CsA \(<2\) mg/kg/day for maintenance are at a low risk of nephrotoxicity. In patients requiring higher doses, a repeat renal biopsy after 2 years of CsA therapy might be useful. When histological signs of nephrotoxicity are documented, switching from CsA to another immunosuppressive drug is suggested. At any rate, we do not advocate long-term treatment with CsA in all patients with lupus nephritis. We feel, however, that the possibility of rotating different drugs in a disease such as SLE, which usually requires long-term treatments, may help in maintaining remission while avoiding iatrogenic morbidity.

In summary, the available data suggest that CsA may be a useful drug in patients with lupus nephritis showing persistent severe proteinuria after induction therapy or intolerance to other immunosuppressive drugs.

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