Long-term effects of cyclosporine A in Alport’s syndrome

LUIS CALLÍS, ANGEL VILA, MARTA CARRERA, and JOSÉ NIETO

Department of Paediatric Nephrology, Hospital Materno-infantil Vall d’Hebron, Barcelona, Spain

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Background. In 1991, our initial results of cyclosporine A (CsA) administration in eight patients with Alport’s syndrome were published. A significant decrease in or disappearance of proteinuria and apparently good tolerance to CsA were observed in all patients.

Methods. CsA administration has been maintained in these eight patients with the aim of obtaining further information about the clinical course of the disease. The ages of these eight patients currently range from 15 to 27 years, and the mean duration of treatment is from 7 to 10 years (x = 8.4 years).

Results. Renal function has remained stable, with no evalu-
able changes in serum creatinine levels compared with pre-
CsA treatment values. Proteinuria in all patients has either remained negative or are values far lower than pretreatment levels. A second renal biopsy was performed in all patients after five years of CsA administration. No aggravation of the lesion present at the first biopsy or lesions typical of cyclo-
sporine intoxication was observed.

Conclusions. After a mean duration of 8.4 years and with no deterioration in renal function, we found possible beneficial effects of the continued treatment of CsA in patients with Alport’s syndrome who present evidence of progression to renal insufficiency.

In 1991, we published a study of the effects of cyclo-
sporine A (CsA) on proteinuria in eight patients with Alport’s syndrome who presented with significant renal involvement [1]. CsA was observed to have a marked and sudden early reducing effect on proteinuria in all of them. Owing to the good patient tolerance to CsA and its persistence of action on proteinuria, administration has been continued up to the present for the purpose of obtaining more information about the potentially positive effects on the clinical course of the disease.

METHODS

The diagnosis of Alport’s syndrome was based on the presence of hematuric nephropathy, a family history of renal involvement, renal insufficiency, neural hearing loss, ocular abnormalities in the propositus or in a relative, and thickening of the glomerular basement membrane by electron microscopy with splitting and splintering of the lamina densa [2–10]. In our experience and that of other authors, the presence of massive proteinuria is suggestive of a poor prognosis toward eventual renal failure [1, 5, 7, 9–12].

Eight patients described in our previous report [1] met these criteria and were selected to receive CsA treatment (after parental consent had been obtained) because of the presence of massive persistent proteinuria (>40 mg/hr/m²). The disease was inherited from the mother in these eight selected patients, and a family history of renal involvement, neural hearing loss, and ocular abnor-
malities was verified in three generations of each family.

The clinical features of these eight patients (mean age of 12.2 ± 4.27 years) at the beginning of the study are shown in Table 1. Arterial blood pressure was normal in all patients except one, who required antihypertensive therapy; seven patients had nerve deafness, and ocular abnormalities were present in two. Creatinine clearance was normal in five patients and was moderately low in the other three; maximum urinary osmolarity was normal in six patients (1025.8 ± 110.4 mOsm/kg) and decreased in two patients with low creatinine clearance (patients 7 and 8; Table 1). Proteinuria was persistent and massive in all of them, ranging from 46 to 207 mg/hr/m².

Since the publication of our first article in 1991 [1], CsA administration has been continued in these eight patients. The initial total daily dose of CsA was 5 mg/kg/day (half of the dose being given every 12 hr), in the search for the optimum dose required to maintain mean levels of 82 ± 13 ng/ml. The present age of these patients ranges between 15 and 27 years, with a mean of 20.1 years, and the duration of CsA treatment currently ranges from 7 to 10 years. During these years of CsA treatment, proteinuria, creatinine clearance, maximum urinary osmolarity, and serum CsA levels were measured every four months. Hearing loss was measured once a year.

Proteinuria was measured by using a 24-hour urine collection by sulfosalicylic acid precipitation and turbi-

Key words: heritable disorders, CsA, proteinuria, renal failure.

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Table 1. Clinical-analytical data at onset and at present

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Features</th>
<th>Age (years)</th>
<th>Length of treatment</th>
<th>Creatinine clearance (ml/min/1.73 m²)</th>
<th>Proteinuria (mg/m²/hr)</th>
<th>MxU Osm (mOsm/kg)</th>
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<td>27</td>
<td>10</td>
<td>207</td>
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<td>410</td>
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</table>

Abbreviations are: N, nerve deafness; BP, hypertension; L, lenticonous. All presented with hematuria. Patient number 3 presented nerve deafness at 10 years of age.

dimetry. Creatinine clearance was calculated from the serum creatinine concentration and rates of creatinine excretion over a 24-hour period. Maximum urinary osmolarity was measured after a 10-hour nocturnal hydropenic period, and urine was investigated for a cryoscopic decrease. CsA was measured in total blood by specific monoclonal radioimmunoassay. Liver function was regularly evaluated.

Two renal biopsies were performed in these eight patients: the first before CsA administration and the second in all patients after four to five years of CsA treatment. Hematoxylin-eosin, periodic acid-Schiff stain, Masson-trichrome, and silver-methenamine were performed on representative sections. Immunofluorescence stains and electron microscopy were also performed.

RESULTS

The first renal biopsy performed before the start of CsA administration showed the following features: moderate or light focal and segmental glomerular hypercellularity on light microscopy in six patients; the remaining two (patients 7 and 8; Table 1) had focal and segmental lesions of the tuft due to marked thickening of the glomerular basement membrane and mesangial matrix associated with hyaline deposits and collagen of capillary loops. Immunofluorescence was negative in all patients. Electron microscopy showed irregular thickening and discontinuity of the glomerular basement membrane, as well as the splitting and splintering of the lamina densa of the glomerular basement membrane in all patients.

After 7 to 10 years of continued CsA treatment, the clinico-analytical situation of these eight patients is as follows: A good general status exists. Arterial blood pressure is normal in seven patients, and the remaining patient (case 8) continues to require two hypotensors for control. Hypoaacusia remains stable in three (cases 1, 2, and 6), has worsened in four (cases 4, 5, 7, and 8), and has appeared in case 3. Endogenous creatinine clearance is normal in five patients (cases 1, 2, 3, 4, and 6) and has not varied noticeably in the remaining three cases (cases 5, 7, and 8) who had been in renal insufficiency prior to the start of the study (Fig. 2 and Table 1). In all of these, macroscopic hematuria has persisted. Proteinuria has ranged from negative (cases 1 and 2) to 20.4 to 50.6 mg/hr/m² in the six remaining cases (Fig. 3 and Table 1). The maximum urinary osmolarity was maintained between 898 and 991 mOsm/kg in cases 1, 2, 3, and 4 and was decreased in the other four cases to 782, 824, 560, and 410 mOsm/kg, respectively (Table 1).

The second biopsy, performed after four to five years of CsA administration, revealed no worsening of the initial lesion, and vascular lesions suggestive that cyclosporine intoxication, such as arteriolar hyalinosis, were not observed. Thus, in cases with minimal mesangial proliferation, this continues to be the same, and focal segmental sclerotic lesions are neither more diffuse nor more generalized in the affected cases. No variations have appeared on immunofluorescence study. Electron microscopy showed irregular thickening and discontinuity of the glomerular basement membrane, and splitting and splintering of the lamina densa of the glomerular basement membrane with the same intensity as observed in the first biopsy (Fig. 1).

DISCUSSION

Our eight patients with Alport’s syndrome fulfill the criteria proposed in the literature as suggestive of rapid and precocious progression to end-stage renal disease: gross hematuria, massive and persistent proteinuria, sensorineural deafness with or without anterior lenticonus, as well as diffuse thickening and multilamellation of the glomerular basement membrane [4, 7, 9, 10, 13, 14]. The effect of CsA on proteinuria in these patients described in our previous report [1] still persists after a 7- to 10-
year treatment period (proteinuria remains negative in two patients and is markedly reduced in the rest). Hypoacusia currently present in all patients has either remained stable or has worsened in three patients. Macroscopic hematuria persists in all of them (Table 1). Blood pressure remains the same, and maximum urinary osmolality has not changed, except in patients 5 and 6, who presented maximum urinary osmolarity of 980 and 920 mOsm/kg prior to CsA and 782 and 804/kg after CsA, respectively. Endogenous creatinine clearance is stable in all; it is of interest to note the findings in cases 5, 7, and 8 in which decreased clearance values were observed at the start of the study and have remained stable since CsA treatment was started 7 to 10 years earlier, contrary to what is normally observed in the natural evolution of the glomerular filtration rate in Alport’s syndrome (Fig. 2 and Table 1) [3, 4, 7, 9]. End-stage renal disease develops in virtually all affected males with X-linked Alport’s syndrome, and several authors have observed that the rate of progression to renal failure is fairly constant among affected males within a particular family [7, 9, 15–17]. Taking this into account and with all due reserve, it was also interesting to compare the creatinine clearance values of our eight patients with those of other members of their respective families who had presented with renal insufficiency (Fig. 4 and Table 2). We were able to verify a marked difference with respect to the chronological time of onset of the renal insufficiency in favor of patients receiving CsA treatment. CsA levels throughout the study were 82 ± 13 ng/ml. There were

Fig. 1. Electron micrograph of patient 5 (2nd renal biopsy). Irregular thickening of the glomerular basement membrane and splitting and splintering of the lamina densa are shown (uranyl acetate × 12,000).
Fig. 2. Creatinine clearance values (ml/min/1.73 m²) at onset and at present.

Fig. 3. Proteinuria values (mg/hr/m²) at onset and at present.

no signs of hypertrichosis or gingival hypertrophy or other more serious side-effects (such as opportunistic infections, malignancies, and so forth). The other element to be assessed in these eight patients was the lack of evolution of the histologic lesion or lesions related to CsA effects. There was no aggravation of the existent glomerular lesion or an increase in interstitial fibrosis. The lesion of the glomerular basement membrane persists in all cases, with the same characteristics in each [

Angiotensin-converting enzyme inhibitors do not reduce proteinuria in patients with Alport’s syndrome as CsA proved to do in our study [1, 20–22]. Mechanisms by which CsA acts on proteinuria in these patients are not clearly defined, although three basic types may be accepted: (a) renal vasoconstriction (renal hemodynamic changes); (b) direct action on the permselectivity of the glomerular basement membranes, particularly on the electrochemical barrier that repels anionic albumin molecules; and (c) the immunological nature that involves lymphokine secretion inhibition [23–36]. All of these different actions would slow down disease progression with no variation in the basic type IV collagen lesion.

Kashtan recently affirmed that a demonstrably effective method of slowing down the progression of Alport’s nephropathy does not exist [13]. However, because mes-
Table 2. Comparative creatinine clearance values in probands and relatives at similar ages

<table>
<thead>
<tr>
<th>Family</th>
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Abbreviations are: ESRD, end-stage renal disease; Ccr, creatinine clearance; ml/min/1.73m².

Fig. 4. Comparative creatinine clearance values in probands and relatives at similar ages. Only the age at end-stage renal failure is shown for relatives of cases 6 and 7. Symbols are: (C–) probands; (· – ·) brother; (· − ·) cousin.

We believe that the persistence of CsA effects on proteinuria and its apparent prolonged action in halting glomerular filtration deterioration, together with verification of the absence of side effects of CsA on renal parenchyma, permit us to continue CsA administration in patients with Alport’s syndrome in whom elements suggestive or demonstrative of progression to chronic renal insufficiency are observed. It may be concluded that CsA delays progression to end-stage renal failure in these patients. However, further studies are required before the general administration of CsA can be recommended in Alport’s syndrome for those patients with adverse prognostic indicators.

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