No clear evidence of ACEi efficacy on the progression of chronic kidney disease in children with hypodysplastic nephropathy—report from the ItalKid Project database

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Abstract

Background. Chronic kidney diseases (CKD) tend to progress to end-stage renal failure (ESRF). As it has been demonstrated that angiotensin-converting enzyme inhibitors (ACEi) have a renoprotective effect in adults with proteinuric disease and may be effective in reducing hyperfiltration and proteinuria, they are also frequently used as anti-progression agents in paediatric patients with CKD despite the lack of data confirming their role in the nephropathies peculiar to children. The aim of this study was to investigate whether patients with hypodysplastic CKD (the most common cause of ESRF in children) treated with ACEi show a significantly slower decline in creatinine clearance (Ccr).

Methods. The analysis was based on the information available in the database of the ItalKid Project, a nationwide, population-based registry of chronic renal insufficiency (CRI) in children in Italy. Of the 822 patients with CRI due to hypodysplasia, we selected those who had been continuously treated with ACEi; the control patients were identified from the same diagnostic group and matched for gender, age and baseline Ccr.

Results. Progression was analysed as the slope of Ccr in a total of 164 patients: 41 cases and 123 matched controls. There were no significant between-group differences in blood pressure, duration of follow-up or pre-study slope of Ccr ($-0.31 \pm 2.26 \text{ vs } -0.33 \pm 3.58 \text{ ml/min/1.73m}^2/\text{year}; P = \text{NS}$). After an average of 4.9±2.3 years, the mean slope of Ccr was 40% lower in the ACEi-treated cases in comparison to controls ($-1.08 \pm 2.08 \text{ vs } -1.80 \pm 4.42 \text{ ml/min/1.73m}^2/\text{year}$), however, this difference was not statistically significant ($P = 0.31$).

Conclusions. We conclude that ACEi treatment does not significantly modify the naturally progressive course of hypodysplastic nephropathy in children and further studies are necessary before such treatment is routinely proposed for anti-progression purposes in children with CKD.

Keywords: angiotensin-converting enzyme inhibitors; chronic kidney diseases; paediatric nephrology; progression

Introduction

A number of experimental studies have demonstrated that angiotensin-converting inhibitors (ACEi) delay the progression of renal disease in patients with chronic renal insufficiency (CRI), but this renoprotective effect was found in adult patients with mainly diabetic [1] and non-diabetic [2–7] glomerular nephropathies. It is not clear whether and to what extent it is mediated by the anti-proteinuric or anti-hypertensive...
The accumulating evidence of the beneficial effect of ACEi in adults has generated considerable expectations concerning the possibility of delaying the progression of chronic kidney disease (CKD) in children and this has been followed by their generalized paediatric use. However, the diseases responsible for chronic kidney diseases (CKD) in children are very different from those found in adults: in particular, glomerular diseases are uncommon causes of CKD (6%), whereas primarily non-proteinuric diseases such as hypodysplasia, with or without urological abnormalities account for as many as 57% of cases [8]. On the basis of these epidemiological premises, the efficacy of ACEi on the progression of CKD in children is questionable. On the other hand, as these diseases are typically associated with a congenital reduction in nephron mass with consequent hyperfiltration, there is certainly a potentially strong rationale for the use of ACEi [9]. Although ACEi are frequently used as anti-hypertensive and anti-proteinuric agents in children too, no single study has assessed their effect on the progressive decline of glomerular filtration rate in this age group, probably because of the low prevalence of the disease and the consequently small series of patients available even in specialized centres.

The aim of this study was to investigate the efficacy of ACEi as anti-progression agents in children with CKD associated with primarily non-proteinuric diseases using the information available in the large database of a nationwide registry of childhood CKD (the ItalKid Project).

Patients and methods

The data used in the present study come from the Italian Pediatric Registry of CKD (ItalKid Project), which includes all patients diagnosed as having a creatinine clearance (Ccr) of <90 ml/min/1.73 m² (calculated according to Schwartz's formula [10]) before the age of 20 years. The general methodology of the ItalKid Project (its organizational structure, reporting procedures and data quality control) has been described in detail elsewhere [8].

As of 1 January 2003, a total of 1352 children had been registered. This study considered 162 patients with CKD due to hypodysplastic nephropathy with or without urological abnormalities (out of a total of 822) who started ACEi treatment during the follow-up (FU) period. After excluding the patients with an age of <2 years (n = 4), a baseline Ccr of <15 ml/min/1.73 m² (n = 10) and an FU duration on ACEi of <2 years with less than three data points (n = 65), as well as those for whom critical data were incomplete (n = 42), the analysed sample consisted of 82 subjects (33 males). Three patients who had never received ACEi, matched by diagnosis, gender, age and baseline Ccr, were selected as controls for each of the 41 cases (n = 123; 99 males). The primary renal diseases responsible for CKD in the population as a whole were hypodysplasia with associated urological abnormalities (n = 141) [vesicourethral reflux (n = 89; 24 cases and 65 controls), posterior urethral valves (n = 35; 7 case and 28 controls), other urinary abnormalities (n = 17; 4 cases and 13 controls)] and isolated hypodysplasia (n = 23; 6 cases and 17 controls).

The demographic, clinical and biochemical parameters considered for the analysis were age, systolic and diastolic arterial blood pressure (BP) and Ccr. BP was analysed for the 30 cases and 74 controls for whom data were available as the gender- and age-specific standard deviation score (SDS) using the reference values of the 1987 Task Force on BP Control in Children [11].

The primary outcome measure was the rate of progression of CKD, which was calculated as the slope of Ccr over time excluding the year in which ACEi treatment was started. To exclude the possibility of a selection bias among the ACEi-treated patients (i.e. the patients showing faster progression may have been more likely to be prescribed ACEi), the pre-study slope of Ccr was calculated in the 24 cases and 66 controls for whom at least three pre-study Ccr determinations were available. The severity of CKD was classified as mild (60–89 ml/min/1.73 m²), moderate (30–59 ml/min/1.73 m²) or severe (15–30 ml/min/1.73 m²) on the basis of the NKF definition [12]. Fast progressors were defined as the patients with a Ccr slope of less than −3 ml/min/1.73 m²/year; slow progressors as those with a Ccr slope of between −3 and 0 ml/min/1.73 m²/year; and non-progressors as those who showed no loss or a gain in Ccr during the FU [13].

Statistical analysis

Unless otherwise specified, the data are expressed as mean values ±SD. The contingency table was analysed using the χ² test. The between-group differences were assessed by means of the Student’s t-test for unpaired data. The within-group comparisons of baseline data with the data after 1 year and during FU were made using the Student’s t-test for paired data or ANOVA as applicable. The BP indicated as FU BP is the mean of the values recorded during the observation period, with the exclusion of the first two measurements (baseline and 1 year). The Ccr slope of each patient was calculated using all of the available Ccr determinations for the corresponding period. The FU considered for the analysis of progression in the cases and controls excluded the first year of observation (during which ACEi treatment was started in the cases). A P-value of <0.05 was considered statistically significant.

Results

The baseline clinical and laboratory parameters of the study population are shown in (Table 1). There were no differences between the cases and controls in terms of the length of FU, age, Ccr or arterial BP, nor in terms of gender or primary nephropathy distributions. In particular, 7.3% of the cases and 11.4% of the controls were hypertensive (systolic and/or diastolic BP >95th centile for gender and age). Thirteen patients (3 cases and 10 controls) were treated with an anti-hypertensive drug other than an ACEi (a calcium or β-blocker) during the study period.
The pre-study Ccr calculated over a mean FU of 4.6 ± 2.4 years (average of 4.9 data points per patient) was not significantly different between the cases and controls: −0.31 ± 2.26 vs −0.33 ± 3.58 ml/min/1.73 m²/year.

One year after baseline, the decline in Ccr was significant in the ACEi-treated group (from 50.9 ± 16.0 to 47.9 ± 17.9 ml/min/1.73 m²; P < 0.005), but not in the control group (from 51.2 ± 16.5 to 49.9 ± 18.3 ml/min/1.73 m²; P = NS). The ACEi-treated group but not the controls showed a significant decrease in systolic arterial BP after 1 year and during FU (Figure 1A), and in diastolic BP only during FU (Figure 1B).

At the end of the FU period (with an average of 5.1 data points per patient), there was no significant difference in the Ccr slope (excluding the first year) between the cases and controls: −1.08 ± 2.08 vs −1.80 ± 4.42 ml/min/1.73 m²/year (Figures 2 and 3). The same was true when the analysis was restricted to the 22 cases with more than 5 years FU and their matched controls (n = 66): −1.20 ± 1.37 vs −2.10 ± 4.66 ml/min/1.73 m²/year.

Analysis of the contingency table by treatment type (ACEi and controls) and disease progression (fast progressors, slow progressors and non-progressors as defined in Methods section) did not reveal any significant distribution in favour of ACEi efficacy (Table 2). Furthermore, when the cases and controls were divided into three groups on the basis of the initial severity of renal impairment (Table 3) the corresponding Ccr slope was never significantly different between the cases and controls although it was systematically steeper in the latter.

Table 1. Baseline characteristics of patients treated with ACEi and controls

<table>
<thead>
<tr>
<th></th>
<th>ACEi</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>41</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>33/8</td>
<td>99/24</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.0 ± 4.1</td>
<td>9.0 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>5.1 ± 1.8</td>
<td>4.9 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (SDS)</td>
<td>0.64 ± 1.02</td>
<td>0.49 ± 0.96</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (SDS)a</td>
<td>0.52 ± 0.89</td>
<td>0.44 ± 1.11</td>
<td>NS</td>
</tr>
<tr>
<td>Ccr (ml/min/1.73 m²)</td>
<td>50.9 ± 16.0</td>
<td>51.2 ± 16.5</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-study Ccr slope (ml/min/1.73 m²/year)a</td>
<td>−0.31 ± 2.26</td>
<td>−0.33 ± 3.58</td>
<td>NS</td>
</tr>
</tbody>
</table>

aThe reported mean values are not based on the whole population because of missing data (30 cases and 74 controls) (see ‘Patients and methods’ section).

ACEi, angiotensin-converting enzyme inhibitors; SBP and DBP, systolic and diastolic blood pressure; SDS, standard deviation score; Ccr, creatinine clearance.

**Discussion**

The results of our study suggest that ACEi treatment does not significantly delay the progressive decline in renal function of paediatric patients with hypodysplastic nephropathy, the most common cause of CRI in

Fig. 1. Systolic (A) and diastolic (B) blood pressure (as SDS) at baseline, after one year and during follow-up in ACEi and controls (data available for 30 cases and 60 controls).
children [8]. Our analysis has a number of important limitations, but it may be useful because of the absence of results from clinical trials regarding the effect of ACEi treatment on glomerular filtration rate in children with CKD (while waiting for the results of the ongoing ESCAPE trial).

Experimental data have demonstrated the efficacy of ACEi in reducing the progressive loss of renal function, but clinical trials supporting this finding are still limited to adult nephropathies [1–7] and it is well known that adult CKDs have very different etiologies, clinical courses and outcomes than those peculiar to children. The studies of the effects of ACEi in adults have mainly concentrated on glomerular and highly proteinuric, acquired nephropathies, whereas childhood CKDs are commonly due to congenital nephropathies [8], more often show tubulo-interstitial involvement (hypodysplasia with or without urological malformations account for almost 2/3 of cases) and are frequently characterized by little or no proteinuria [14]. As ACEi tend to be more effective in highly proteinuric adult patients [15], it is perhaps not surprising that ACEi-treated children with low proteinuric CKD do not show a significant improvement in terms of disease progression.

It is also important to underline that hypertension is an important and common feature of adult CKD and, together with proteinuria, has been identified as a major contributor to progressive kidney damage [16]. In children, hypodysplastic nephropathies are often associated with salt-losing syndrome and normal or even low BP [17] and, when present, hypertension only develops during the most advanced stages of CRI. The overall prevalence of hypertension in our study population was as low as 10% (perhaps partially because of the exclusion of patients with Ccr of <15 ml/min).

These differences between adult and paediatric CKDs (primary causes, proteinuria levels and the prevalence of hypertension) may explain why we found ACEi to be ineffective in children.

While reporting the results, we feel it is important to discuss the many limitations of our study. First of all, as the study was not prospective and randomized, it could be suspected that the patients receiving ACEi were prescribed them precisely because their disease was more rapidly progressive (selection bias); however,
ACEi and the progression of CKD in children

Given the identical pre-study Ccr slopes in the cases and controls (Table 1), this concern does not seem relevant. Secondly, our database lacks details concerning drug types and dosages and the patients’ treatment compliance cannot be investigated. However, the significant decrease in Ccr during the first year of FU (functional effect of ACEi) and the decrease in both systolic and diastolic BP (Figure 1) not observed in the controls, provides indirect evidence that the cases were actually receiving effective ACEi treatment.

A third weak point of the present analysis is related to the fact that the ItalKid Project only records data on an annual basis, and so the calculation of the slope of Ccr relies on limited observations. However, in our opinion, the average 5-year FU was sufficiently long to ensure the reliability of the results, which is further supported by the fact that the same finding of no significant ACEi efficacy was confirmed when the analysis was restricted to the patients with an FU of more than 5 years. Just in order to count upon a fairly long mean observation period, a high number of patients had to be excluded (65 out of 162) because of a too short period in ACEi. A significant increase in the prescription of ACEi by Italian paediatric nephrologists had taken place in the year 2000 [18] and by the time of the present analysis a substantial number of patients had just started the treatment.

Another major limitation is the lack of information concerning proteinuria, which was not systematically reported to the ItalKid database. As a consequence, it was not feasible to test the possibility that the patients with higher proteinuria levels may have benefited from ACEi treatment. It is well known that ACEi reduce urinary protein excretion in children with hypodysplastic nephropathy [19–20] but, although often done in the case of adult nephropathies [21], the use of proteinuria as a surrogate marker of disease progression may be misleading because the ultimate target of anti-progression treatment should be to stabilize the glomerular filtration rate rather than merely reduce urinary protein excretion. Particularly in the case of CKDs characterized by low proteinuria levels, the loss of urinary proteins may be an effect rather than the cause of disease progression, and any intervention on the effect may well not lead to any benefit on the cause.

The negative findings of the present study can be theoretically explained by the poor sensitivity of the methodology used, which may have been incapable of detecting a marginal efficacy of ACEi. Our study population clearly showed a slow progression rate (a mean loss of Ccr of 0.2 ml/min/1.73 m²/year) and this may make detecting efficacy more difficult than in the case of a faster decline in renal function. It seems important to underline that the slope of Ccr over time during the pre-study period becomes substantially steeper during the study period (as much as 6 times steeper) because in the meantime several patients have entered pubertal age (mean age at study end 11.4 years); it has been previously observed that puberty is normally responsible for a faster decline in renal function [8].

In conclusion, the intervention with ACEi failed to provide the expected effect since the mean Ccr at baseline was 50.9 ± 16.0 and 51.2 ± 16.5 ml/min/1.73 m², respectively in treated and untreated patients and became 43.7 ± 21.2 and 44.8 ± 23.3 ml/min/1.73 m² at the end of the observation period; although the difference in mean slope of Ccr over time (−1.08 vs −1.80 ml/min/1.73 m²/year) seemed clinically promising, this was not statistically significant. Interestingly, the accumulating evidence of the beneficial effect of ACEi in adult patients with CKD has led paediatric nephrologists to make generalized use of them in children; however, we could not identify any clear evidence of short-term ACEi efficacy in reducing the progressive decline in the renal function of children with hypodysplastic CKD. This suggests that using ACEi for anti-progression purposes in such patients should be still considered an experimental treatment and, as such, its prescription should continue to be subject to essential safety and efficacy surveillance. The scientific paediatric nephrology community should continue to encourage, promote and support well-designed and prospective studies of this important aspect of CKD in children.

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