

Does addition of an ARB maintain GFR in children with CKD on ACEi?

Introduction:

A majority of children with chronic kidney disease (CKD) experience a deterioration of their renal function over time. The speed of the deterioration varies from nil to a reduction of $6\text{ml}/\text{min}/1.73\text{m}^2/\text{year}$ (1). The rate of deterioration is related to the amount of proteinuria and the child's blood pressure. Renal function often gets worse during puberty.

This deterioration will inevitably mean that the children will develop end stage renal failure (ESRF) with a need for dialysis and/or transplantation. Delaying and in some cases possibly preventing ESRF is thus an area of great importance in paediatric nephrology.

In adult patients it has since long been clearly shown that treatment with an ACEi will reduce proteinuria by on average 50% and slow down the speed of deterioration of kidney function (2). Published data in children are so far lacking but will most likely be available during this year when the large multicentre study (the ESCAPE study, 3) involving close to 400 children treated with an ACEi will present their results.

Provisional results from ESCAPE show that children treated with ACEi significantly reduce their proteinuria (Wühl personal communication). After one year of treatment, urine protein levels started to increase again and after three years urine protein, whilst lower, was not significantly different from baseline values.

ESCAPE showed that ACEi treatment in children slowed the progression of CKD and this beneficial effect was related to the degree of reduction of the proteinuria. The pre-treatment mean slope of GFR was $-2.6\text{ ml}/\text{min}/1.73\text{m}^2/\text{year}$ which was reduced to a mean slope of $-1.6\text{ ml}/\text{min}/1.73\text{m}^2/\text{year}$, an improvement of some 40%. Children with a mean onset proteinuria of $0.5\text{mg}/\text{mg}$ (approximately equivalent to $40\text{-}50\text{mg}/\text{mmol}$ and albuminuria of $20\text{-}25\text{mg}/\text{mmol}$) showed a benefit from the treatment (Wühl and Schaeffer personal communication).

Studies in adults have shown that the addition of an Angiotensin II receptor blocker (ARB) to the ACEi treatment could, on average, further reduce the proteinuria by some 50% with associated additional retardation of CKD (4). There are small studies in children showing the feasibility of this combination in further reducing proteinuria but there are no studies on progression of kidney function (5,6).

Aim:

The aim is to study if the addition of an ARB to the treatment with an ACEi in children with chronic renal failure will further retard the rate of progression of their renal failure.

Study outline:

Primary outcome measures:

1. The difference between baseline and end of study urine albumin excretion
2. The difference between baseline and end of study GFR.

Secondary outcomes:

1. The difference in side effects with special emphasis on acute increase in serum creatinine or potassium will be compared between the two groups.
2. Any change in haemoglobin levels will be monitored.
3. The number of children experiencing clinically significant symptoms of low blood pressure will be recorded

Inclusion criteria:

1. Children with CKD of any aetiology
2. Ages 5-15 years (Children with CRF below the age of 3 years have been shown to, in a majority of cases, have an improvement of their eGFR until a mean age of 3.2 years) (1).
3. eGFR (calculated with the Schwarz formula) (7) between 20 and 60 ml/min/1.73m²
4. Proteinuria defined as a urine albumin/creatinine ratio of more than 20mg/mmol (protein/creatinine ratio > 40mg/mmol).

Exclusion criteria:

1. Renovascular disease
2. Pregnancy
3. Previous adverse reaction to ARB or ACEi
4. Child or family who in investigator's opinion are not able to comply with the trial protocol

Albuminuria measurements:

To improve these crucial measurements in the study they should be done by a centralised laboratory.

ACEi treatment:

The children will all be treated (or convert if already on ACEi) to a standardised dose (see below) of lisinopril. Although enalapril is widely used, lisinopril has a longer half-life and therefore provides better 24 hour coverage. The dose should be standardised before entering the study and the dose in all children should before randomisation be increased to 0.6 mg/kg or maximum of 40mg/day. This is to assure that the treatment effects of the ACEi treatment have been maximised before entering the child in the study and starting a further drug. Studies in adults have previously been criticised on this aspect.

Randomisation:

The children will be randomised to treatment with Irbesartan or placebo. Before randomisation the children will be stratified according to degree of albuminuria, blood pressure centile and according to the diagnosis of their CKD: congenital malformations or other causes.

Irbesartan treatment:

Starting dose shall be 2mg/kg/dose. This dose should be increased until the urine albumin excretion is below 20mg/mmol or the patient is unable to tolerate a higher dose (hyperkalaemia, hypotension other ADR). During the dose escalation phase the children should be seen on a monthly bases. The maximum needed or tolerated dose or a maximum dose of 150 mg/day below 13 years of age and 300mg/day 13 years

and above should be reached within 3 month time. After each dose increase the creatinine and serum potassium should be monitored after 7-14 days.

Blood pressure control:

The children in the study should be kept with a blood pressure below the 90th percentile for age, sex and height (8).

DNA sampling:

As an additional study the parent/carer will at randomisation also be asked to allow an aliquot of the child's baseline blood sample to be stored for later DNA analysis. This will be used for studies on modifying genes that potentially can explain individual differences in progression of CKD. The child can take part in the main study without participating in the DNA study.

Follow up:

The children should be monitored every 2-3 month for 3 years with measurement of serum creatinine, electrolytes, urine albumin excretion, full blood count and blood pressure. For the children with GFR in the lower study range this will be similar to their clinical needs. Children with a GFR around 50 to 60 ml/min/1.73 m² at onset of the study will due to the study need more visits then they would normally have had. The children will, after each change in Irbesartan dose, need to have the serum creatinine and potassium monitored within 7-14 days.

An increase in creatinine after increasing the ARB dose of up to 25% is regarded as acceptable for the study. Plasma potassium > 6mmol/l in a non-haemolysed blood sample should lead to at least a temporary reduction of the study medication and possibly stopping the ARB according to the judgement of the treating physician. Further diet changes and/or treatment with diuretics may allow re-introduction of the previous dose(s).

Power calculation and numbers to include:

Formal statistical advice was sought from Professor Tim Cole. The formula below was used to calculate the power and number of children needed for the study.

$$n = 16/f^2$$

n is the number of children needed in each group

f= reduction expected to achieve/SD

The number of children needed to achieve an 80% power with a significance level of 0.05 will thus depend on how good therapeutic response we expect to get. I have from the ESCAPE data estimated this to be between 40%.

The mean slope among children with a GFR between 20 and 60 ml/min/1.73m² and albuminuria of more than 20mg/mmol was 4.1 (SD 3.8)(Gonzalez. personal communication).

The number needed in each group was calculated to be 87. Assuming a 20% drop rate during the study an inclusion of 105 children in each study arm will be needed.

Safety monitoring:

A safety committee will monitor the progression of the study. If unacceptable side effects occur the study might be stopped prematurely. The progression of renal failure will be compared between the two groups every six-month and if a significant difference between the two groups occurs before the end of the study the safety monitoring group might stop the study and break the code. This is to assure that children who are treated with placebo will not be denied effective treatment longer than necessary if a beneficial effect of the ARB treatment is found.

Importance:

It is of major importance to evaluate the potential benefit, if any, of ARB treatment in children with CKD. This is likely to be a treatment that is increasing in children during the coming years. This will then be only based on data in adults and it is crucial to get childhood data to support, or not, the use of this treatment in children.

Working group:

The group that has worked on this draft study protocol has been: Caroline Booth, Evelina's Childrens Hospital, Joanna Clothier SpR Birmingham Children's Hospital, William van't Hoff, Great Ormond Street Hospital for Children and Dr Philip Kalra, Nephrology Unit, Hope Hospital, Salford.

References:

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Outstanding issues to discuss within BAPN:

1. Should we measure albuminuria or proteinuria. This does most likely not make a big difference. More important is to have centralized measurements.
2. Do we want to also centralise creatinine measurements? Or calibrates the different laboratories?