Alport Syndrome and Thin Membrane Disease

Prof. Dr. M. Weber
PD Dr. R. Girgert
D. Rubel

Prof. Dr. Oliver Gross
Nephrology&Rheumatology
University Medicine Goettingen
gross.oliver@med.uni-goettingen.de
www.alport.de
Disclosure

Initiator and PI of phase 3 clinical trial in children with Alport syndrome (sponsored by German Government)

PI for Germany in ATHENA and HERA study in Alport syndrome (sponsored by Regulus Therap. Inc.)

PI for Germany in CARDINAL study in Alport syndrome (sponsored by Reata Pharmaceuticals)
1. The medical problem: Alport Syndrome

2. From bedside to bench: Alport animal model
   nephroprotective therapy in mice

3. … and back to bedside: Alport registry
   therapy in man delays renal failure and improves life-expectancy

4. Evidence based medicine in a rare disease??
   randomised, placebo-controlled EARLY PRO-TECT Alport trial

5. Future medical therapy
   upcoming clinical trials

6. Sum up for daily clinical practice
Gene-frequency: X-chromosomally 1:5000 to 1:10000, autosomally 1:50,000; 1% of patients on dialysis

Gene-frequency of autosomal heterozygous patients (with thin basement disease):
1% of the TOTAL population, >1% of patients on dialysis, >5% of patients with CKD

A.C. Alport 1927 first mentioned in literature

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>Gene Mouse</td>
<td>2000-2003</td>
<td>RAAS in mouse</td>
</tr>
<tr>
<td>1996</td>
<td>Mouse</td>
<td>2006-2012</td>
<td>RAAS</td>
</tr>
<tr>
<td>2000-2003</td>
<td>RAAS in mouse</td>
<td>2006-2012</td>
<td>RAAS</td>
</tr>
<tr>
<td>2006-2012</td>
<td>RAAS in humans</td>
<td>2017</td>
<td>new meds</td>
</tr>
</tbody>
</table>
Organ-specific distribution of type IV collagen chains

Hudson, NEJM 2003
Consequences

Age at onset of end-stage renal disease

Renal function

100%
75%
50%
25%

Dialysis
Dialysis
Dialysis

healthy

untreated
1. The medical problem: Alport Syndrome

2. From bedside to bench: Alport animal model

*nephroprotective therapy in mice*
Early Ramipril therapy delays renal failure in mice
Value of proteinuria and timing of therapy in Alport’s

Pathogenesis of type IV collagen diseases: interstitial fibrosis
1. The medical problem: Alport Syndrome

2. From bedside to bench: Alport animal model
   nephroprotective therapy in mice

3. … and back to bedside: Alport registry
   therapy in man delays renal failure and improves life-expectancy
Delay of renal failure: the earlier the better?

Gross, Kidney Int 2012

283 patients, 3 generations, mean duration of therapy >5 years
mean retrospective follow-up >20 years
... sibling pairs: the younger brother does better!
… and prolongs life-expectancy

... confirmed in ERA-EDTA registry

Age at start RRT
median: 33.8
median: 26.6
median: 26.3
median: 27.4

Date of RRT initiation
Age of RRT initiation
Alport patient
Spline curve

+ 6.4 years

Temme et Gross, CJASN 2012
Add on therapy currently used in Alport syndrome

ACE-inhibitor
- ? additive effect?
  - ACE-inhibitor plus AT1-antagonist

Ca-antagonist

Aldosterone-antagonist

Paricalcitol

Statin
- HMG-CoA-reductase-inhibitor
- severe genotype (frameshift, large deletion, etc.)

delay of renal failure
- cardiovascular risk
- hearing loss

life-style:
- obesity & no sports
- high (animal) protein intake
- high sodium intake
- ? loud music and hearing loss?

Annex:
- additional (renal) disease
- recurrent bacterial infections
- poor dental health
- ? nephrotic range proteinuria?
- nephrotoxic medication
- analgetics (NSAR)
- smoking

Deltas, Perin, Gross, *NDT 2014*
multi-target approach to a lifelong delay of renal failure

Jeff Miner
Dominic Cosgrove
Billy Hudson
Karl Tryggvason

Kruegel, Rubel, Gross Nat Rev Nephrol 2013
1. The medical problem: Alport Syndrome

2. From bedside to bench: Alport animal model jurisprudence therapy in mice

3. ... and back to bedside: Alport registry therapy in man delays renal failure and improves life-expectancy

4. Evidence based medicine in a rare disease??
   
   randomised, placebo-controlled EARLY PRO-TECT Alport trial
Do the retrospective data justify RAAS-blockade?

- Bias towards less severe mutations
- Loss of follow up
- Selection bias by reporting nephrologists
- Less data in patients, who do not like to go to nephrologists
Early prospective Therapy Trial to Delay Renal Failure in Children with Alport Syndrome

Ramipril versus Placebo

Coordinating Principal Investigator: Prof. Dr. Oliver Gross

EudraCT Number: 2010-024300-10
Protocol: Version 2.0, 28 February 2012

Trial Office
O. Gross, J. Krügel, F. Weber
UNIVERSITY MEDICAL CENTER GÖTTINGEN
Dept. of Nephrology and Rheumatology
Robert-Koch-Str. 40
37075 Göttingen, Germany
Tel: +49 (0)551 - 39-6910
Fax: +49 (0)551 - 39-6911
Email: studie@alport.de
Homepage: www.alport.de/EARLY_PROTECT_Alport

Sanofi-Aventis provides Ramipril & Placebo

and Nick Kidney

GPN-supported trial
USA helps out with observational data
**Endpoints**

**Goal:**
Safety and Efficiency of the ACE-inhibitor Ramipril in delaying the course of Alport syndrome in children with early stages of disease

Randomisation of **80 children** need to achieve a reasonable power

**Overall-Time-On-Therapy** with Ramipril ~270 patient-years

**Primary Efficiency End Point:**
Time to next level of disease within 3 years of Ramipril-therapy compared to Placebo, for all randomised patients.

Estimated: 50% in Placebo-Group  
20% in Ramipril-Group

Very strict criteria for „progress of disease“ to avoid disadvantages for the Placebo-Group

**Treatment Phase up to 6 years (!) Results in spring 2019**

**EMA contributes by scientific advice and safety data**
1. The medical problem: Alport Syndrome

2. From bedside to bench: Alport animal model
treatment in mice

3. ... and back to bedside: Alport registry
treatment in man delays renal failure and improves life-expectancy

4. Evidence based medicine in a rare disease??
randomised, placebo-controlled EARLY PRO-TECT Alport trial

5. Future medical therapy
upcoming clinical trials
FEEDBACK
PSYCHOLOGICAL IMPACT

CLINICIANS! GIVE ACCESS TO PSYCHOLOGICAL COUNSELLING

MEASURE THE IMPACT IN CLINICAL TRIALS

SHARED EXPERIENCES

the whole journey

HEARING LOSS
CHRONIC KIDNEY DISEASE
POST TRANSPLANT
PREGNANCY
FAMILY PLANNING
CHILD TO ADULT TRANSITION

VIDEO INTERVIEWS WITH ALPORT FAMILIES
ALPORT SYNDROME
- A CLINICIAN'S VIEW
CLIFFORD E. KASHTAN

NEW GROUPED CLASSIFICATION
COLLAGEN IV & 345
ALPORT
XLAS ARAS
HETEROZYGOE HETEROZYGOE
ADAS COL4A3/4 COL4A5
TMBM ARAS CARRIER

IDENTIFY + VALIDATE BIOMARKERS
+ OPEN ACCESS TO DATA

WE HAVE A SHARED VISION...

WE NEED:

BRING BACK HOPE
TREATMENTS TO PATIENTS

CONSIDER RISKS IN TESTING
THERAPIES
PRICING MUST BE
AFFORDABLE

WHAT ROLE CAN WE PLAY?

THINK STRATEGICALLY

WE WANT YOU TO:
GET SPECIFIC

ALPORT SYNDROME
- A PATIENT'S VIEW
SHARON LAGAS
<5% risk of anti-GBM disease
anti-GBM antibody screening in 1st year post Tx
diagnostic workup in type IV collagen diseases

**Start diagnostic workup in:**
1. any child with renal hematuria
2. any child with suspected carrier-status
3. young patient with FSGS (without EM)
4. any patient with proteinuria
5. elderly patient with „chronic GN“
6. family history of hematuria or renal failure

**Diagnosis:**
1. hematuria
2. family history
3. inner ear hearing impairment
4. ocular changes

**Kidney biopsy** always including EM

**Type IV collagen immunostaining of skin/kidney**

**Molecular genetic** plus genetic counselling

**Type IV collagen disease**

- **Alport Syndrome**
  - heterozygous Alport-carrier
  - thin basement membrane
more than 400 years ... familial benign hematuria?

Forfathers moving from Südtirol to Saarland for religious reasons and looking for employment in ~ 1620 (30-years war in Europe)

~ 300 years

10 sons and following generations stay in same area for employment reasons (working as miners)
(total population in area ~ 40,000 people in 1990)

For generations, family members are known to have sporadic episodes of macrohematuria

A

B

C

D

Exon 24
Deletion 184 bp

Exon 25

Allel 1

Exon 24
Deletion 18 bp

Exon 25

Allel 2

= hematuria
= renal insufficiency
= deafness
= hypertension

= DNA available for study

Gross, NDT 2004
Diagnosis

- 1. hematuria
- 2. family history positive
- 3. hearing loss
- 4. ocular changes

**Kidney biopsy always** including EM or **Moleculargenetic** testing

! Please report every patient to national or international Alport-registry !

**Alport-Syndrome**

- Hematuria or Micro-Albuminuria

**ACE-inhibitor**

- EARLY PRO-TECT Alport-Study

**heterozygous Alport-patient**

- Proteinuria >0.3g/day

- yearly follow-up for risk-factors & proteinuria

- consider therapy

**ACE-inhibitor**

- NO Risk

- Hematuria or Micro-Albuminuria

- Proteinuria >0.3g/day

- NO Risk

- Statins

- Paricalcitol

**thin basement membrane**

- YES Risk

- Hematuria or Micro-Albuminuria

- Proteinuria >0.3g/day

- YES Risk

- HERA

- CARDINAL

If progress use add-on therapy:

- AT1-Antagonist
- RR-target below 125/75 mmHg
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Inclusion criteria</th>
<th>Recruitment</th>
<th>Expected end</th>
</tr>
</thead>
<tbody>
<tr>
<td>EARLY PRO-TECT Alport NCT01485978</td>
<td>Phase 3, double-blinded Placebo controlled Interventions: - Ramipril vs. Placebo End-points: - Safety - Progress of albuminuria</td>
<td>Age 2-17 years Classical Alport only Very early stages only - Micro-Hematuria - Micro-Albuminuria - GFR&gt;90/ml/min/1,73m²</td>
<td>closed 9/2015</td>
<td>Start 2/2012 End 8/2019</td>
</tr>
<tr>
<td>HERA NCT02855268</td>
<td>Phase 2, double-blinded Placebo controlled Interventions: - anti-microRNA21 vs. Placebo End-points: - eGFR-loss</td>
<td>Age 16-60 years GFR&lt;90</td>
<td>Expected start summer 2017</td>
<td>? 2019</td>
</tr>
<tr>
<td>CARDINAL NCT03019185</td>
<td>Phase 2/3, double-blinded Placebo controlled Interventions: - Bradoxolone Methyl vs. Placebo End-points: - eGFR-loss</td>
<td>Age 12-60 years GFR&lt;90</td>
<td>Expected start summer 2017</td>
<td>? 2019</td>
</tr>
<tr>
<td>ATHENA NCT02136862</td>
<td>nicht-interventional observational study Interventions: End-points: - eGFR-loss</td>
<td>Age 16-65 years GFR&lt;90</td>
<td>Until 2017</td>
<td>? 2019</td>
</tr>
<tr>
<td>European Alport Registry NCT023788805</td>
<td>nicht-interventional observational study Interventions (observed): - RAAS-blockade and Spironolacton - Statins - Paricalcitol End-points: - end stage renal failure - death</td>
<td>Age 0-99 years All stages including end-stage</td>
<td>Until 2038</td>
<td>Start 2006 End 2038</td>
</tr>
</tbody>
</table>
Conclusions

Possible life-long delay of renal failure in patients with co-incidence of early diagnosis and missense-mutations?

Yearly follow-up by nephrologist – up to 20 years gain of kidney function.
Embryogenesis of GBM and Alport pathogenesis provide crucial therapeutic targets for all chronic kidney diseases

ALL type IV collagen diseases have a risk of ESRF (X, a.d., a.r.) check for risk factors, yearly follow up in all patients

Alport syndrome has become a treatable disease in a combined effort by patient-groups, researchers and clinicians

ACE-inhibitor therapy delays renal failure (?the earlier, the better?) and improves life-expectancy

Earlier therapy (hematuria/micro-albuminuria) in children only in controlled trials (EARLY PRO-TECT Alport)

**strong need** for early diagnosis in children (ESPN & patient groups)
Conclusions II

RAAS-blockade in all patients and carriers at risk
„add on“ includes ACE+AT1, Aldo, Ca-ant., statins, Paricalcitol

good prognosis post Tx, watch for anti-GBM in first year

all expert recommendations are off-label – need for registries

new therapies on the horizon (and old ones to be evaluated)
  hope for a lifelong delay of renal failure and co-morbidities

we all need new therapies and the (financial) interest of industry

Expert recommendations will get in conflict with future „new“ FDA-approved therapies – needs to be addressed by FDA/EMA
Thank you

gross.oliver@med.uni-goettingen.de

Deutsche Nierenstiftung
DFG GR 1852/4-1, 4-2, 6-2

www.alport.de

Fritz-Scheler Stipendium
GPN, BMBF, NIH