Alport Syndrome
A treatable hereditary kidney 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
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)
Agenda

1. Nephroprotective Therapy in Alport Mice

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

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

4. Future medical therapy upcoming clinical trials

5. Sum up for daily clinical practice
Pathogenesis of Alport’s syndrome

Hudson, NEJM 2003
Heterozygous and homozygous Alport’s syndrome: a clinical spectrum of one type IV collagen disease
Pathogenesis of type IV collagen diseases: solely mechanics?
Early Ramipril therapy delays renal failure in mice

Value of proteinuria and timing of therapy in Alport’s

proteinuria is not a good end point in Alport’s

multi-target approach to a lifelong delay of renal failure

1. 7S
2. collagen receptors
3. cell based therapies
4. Repair of GBM
5. Anti-miRNA-21

Jeff Miner
Dominic Cosgrove
Billy Hudson
Karl Tryggvason

Collagen receptor
- altered signal

ACE inhibition

TGF-β, MMPs, TIMPs, CTGF, chemokines

Podocyte

Secondary nephrosclerosis
ESRD
Fibrosis

Kruegel, Rubel, Gross Nat Rev Nephrol 2013
Add on therapy currently used in Alport syndrome

ACE-inhibitor
- ? additive effect?
- ACE-inhibitor plus AT1-antagonist
- Paricalcitol
- Statin (HMG-CoA-reductase-inhibitor)

Ca-antagonist

Aldosterone-antagonist

Renin-antagonist

Additional (renal) disease:
- recurrent bacterial infections
- poor dental health
- nephrotic range proteinuria?

Severe genotype:
- (frameshift, large deletion, etc.)

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

Factors:
- cardiovascular risk
- hearing loss

Factors:
- delay of renal failure
- nephrotoxic medication
- analgetics (NSAR)
- high blood pressure
- smoking

Deltas, Perin, Gross, *NDT 2014*
1. Nephroprotective Therapy in Alport Mice

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

283 patients, 3 generations, mean duration of therapy >5 years mean retrospective follow-up >20 years

ALPORT SYNDROME
- A CLINICIAN’S VIEW
CLIFFORD E. KASHTAN

NEW GROUPED CLASSIFICATION
COLLAGEN IV & 345 ALPORT
XLS AS ARAS
HETEROZYGOTE COL4A3/4
ADAS TGDN
HETEROZYGOTE ARAS CARRIER

IDENTIFY + VALIDATE BIOMARKERS
+ OPEN ACCESS TO DATA

CONSIDER RISKS IN TESTING THERAPIES
PRICING MUST BE AFFORDABLE

WE HAVE A SHARED VISION...

BRING BACK HOPE
TREATMENTS TO PATIENTS

WHAT ROLE CAN WE PLAY?

THINK STRATEGICALLY

WE WANT YOU TO: GET SPECIFIC

ALPORT SYNDROME
- A PATIENT’S VIEW
SHARON LAGAS
1. Nephroprotective Therapy in Alport Mice

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

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

Sanofi-Aventis provides Ramipril&Placebo

and Nick Kidney

GPN-supported trial

GPN-Gesellschaft für Pädiatrische Nephrologie
UNIVERSITÄTSMEDIZIN GÖTTINGEN

GPN-Protected Trial
USA helps out with observational data
Rationale

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

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
Agenda

1. Nephroprotective Therapy in Alport Mice

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

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

4. Future medical therapy
   upcoming clinical trials
FEEDBACK
PSYCHOLOGICAL IMPACT

CLINICIANS! GIVE
ACCESS TO PSYCHOLOGICAL COUNSELLING

MEASURE THE IMPACT IN CLINICAL TRIALS
VIDEO INTERVIEWS WITH ALPORT FAMILIES

SHARED EXPERIENCES
## Clinical Trials in Alport Syndrome in 2017

<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 PROTECT 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;90ml/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  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 NCT02378805</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>
<tr>
<td>ASTOR NCT00481130</td>
<td>nicht-interventional observational study</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Nephroprotective Therapy in Alport Mice
2. … and back to human: Alport registry therapy in man delays renal failure and improves life-expectancy
3. Evidence based medicine in a rare disease?? randomised, placebo-controlled EARLY PRO-TECT Alport trial
4. Future medical therapy upcoming clinical trials
5. Sum up for daily clinical practice
! Please report every patient to national or international Alport-registry!

- Alport-Syndrome
  - Hematuria or Micro-Albuminuria
    - EARLY PRO-TECT Alport-Study
      - If progress use add-on therapy:
        - AT1-Antagonist
        - RR-target below 125/75 mmHg
        - Statins
        - Paricalcitol

- heterozygous Alport-patient
  - Proteinuria >0.3g/day
    - ACE-inhibitor

- thin basement membrane
  - screen for additional risk factors such as high blood pressure, smoking, additional renal diseases, diabetes, nephro-toxic medications
  - NO Risk
    - Hematuria
  - YES Risk
    - Hematuria or Micro-Albuminuria
      - yearly follow-up for risk-factors & proteinuria
      - consider therapy
        - ACE-inhibitor
  - Proteinuria >0.3g/day

Studies with new Medications:
- HERA
- CARDINAL
**Conclusions**

- **Early Diagnosis** vs **Late Diagnosis**
  - **Early Diagnosis**: $x$ years earlier diagnosis – 3x years gain of kidney function
  - **Late Diagnosis**: Very late diagnosis

- **Possible Life-long Delay**
  - 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
  - 20 years!!

**Age at Onset of End-stage Renal Disease**

- 10
- 22
- 30
- 40
- 50
- 60
- 70
- 80

- **Renal Function**
  - 100%
  - 75%
  - 50%
  - 25%
  - 10%

- **RAAS Protection**
  - Lifestyle
  - Unknown
Thank you
gross.oliver@med.uni-goettingen.de