What’s new in TSC???

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BASICS TSC

• TSC is a rare autosomal dominant genetic disorder (1/8000) characterised by development of benign tumours and lesions in various organs

• TSC is caused by mutations in the TSC1 or TSC2 tumour suppressor genes, which code for hamartin and tuberin, respectively

• Hamartin and tuberin form a complex that indirectly inhibits the activity of the mechanistic target of rapamycin (mTOR)
Basic genetics of TSC

**TSC1**: 23 exons, 130 kDa protein, 1,164 aa

**TSC2**: 41 exons, 200 kDa protein, 1,807 aa

- Autosomal-dominant ~ 100% penetrance
- More than 2,000 non-synonymous mutations have been identified in **TSC1/TSC2** genes
  - 50–60% of all mutations are single-base substitution mutations (C < T)
  - large rearrangements: 6% **TSC2**, 0.5% **TSC1**
- 10–15% NMI
- 2/3 are *de novo* mutations
- Only genotype–phenotype correlation
  - CGS
  - some missense mutations in **TSC2**-mild

MUTATIONS IN TSC

- Identified in 70-90%. Otherwise NMI. Cause? Non coding regions/ Mosaicism mostly

Most TSC1 and TSC2 mutations result in premature termination of translation
NGS in TSC

ADVANTAGES:
- Lower cost
- Quicker
- Mosaicism can be detected

DRAWBACKS:
- Large in/del
- High number of variants per individual (prioritisation). No functional test available. Difficulty classifying variants. Patient derived cells for RNA-based studies would greatly facilitate these studies
- Mosaics may be missed in regions with low coverage
- Wait for large number of individuals to be tested in a single run to optimize cost (avoided with panels)
MOLECULAR PATHOLOGY OF TSC

Loss of Heterozygosity (LOH)²

Inactivation of second allele of TSC1 or TSC2%

Mutant TSC1/2% allele

Mutant TSC1/2% allele

Haploinsufficiency²

Inactivation of a single allele of either TSC1 or TSC2%

Normal TSC1/2% allele

Mutant TSC1/2% allele

Mutation of either TSC1 or TSC2 disrupts the TSC1–TSC2 complex, resulting in hyperactivation of mTOR¹,²
TSC is SYSTEMIC disease

Major features
1. Hypomelanotic macules (3, at least 5-mm diameter)
2. Angiofibromas (3) or fibrous cephalic plaque
3. Ungual fibromas (2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)
11. Angiomyolipomas (2)

Minor features
1. “Confetti” skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartoma

Northrup et al, Pediatric Neurology 49 (2013) 243e254
CLINICAL PRESENTATIONS OVER TIME

- Rhabdomyomas
- Cortical tubers
- SENs / SEGAs
- Renal and hepatic manifestations
- Dermatologic manifestations
- Retinal hamartomas
- Oral manifestations
- LAM
CLINICAL FEATURES OF TSC

Images courtesy of John J. Bissler, MD.
Renal involvement in TSC

**CYSTS**
- No clinical repercussion except for the contiguous gene syndrome: CGS
  - **TSC2/PKD1**
- More frequent with **TSC2** mutations

**ANGIOMIOLIPOMAS (AML)**
- More frequent and severe in **TSC2**
- Clinical repercussion

**RENAL CANCER**
- Infrequent
- Difficult to diagnose
A- Glomerulocystic disease. Infrequent but not easy to diagnose

B- Simple cysts: micro/macro: 30-50% of patients

C- CGS TSC2/PKD1

Modified from Bissler et al 2010 Pediatr Nephrol
Renal Cysts in Patients With TSC

2–5% of TSC patients:
Severe, very early onset PKD
Significant CKD in teenage years

TSC2/PKD1 contiguous gene deletion Sd

Torra R et al 1998
AMLs in Patients With TSC

AML represent 1-2% of all renal tumors. 0.13% of population have AML. 20% of patients with AML have TSC.

AMLs develop in up to 80% of patients with TSC

- Multiple and bilateral renal tumors
- 8.6 years = median age of initial AML detection
- Benign hamartomas rich in fat, blood vessels, and smooth muscle
- May occur in other organs

Pericyte origin of TSC-associated AML

- Pericytes are mesenchymal perivascular cells attached to the abluminal surface of capillaries.
- Specific functions in regulating microvascular stability, development, and function
- AML cells, like pericytes, histochemically express α-SMA and pericytes also can accumulate lipid, as is seen in AML

Pericyte origin of TSC-associated AML

Decreased renal AML development in:

- Patients with CGS TSC2- PKD1 treated from an early age with ACEI or ARBs due to HBP

**TSC-associated AML**

- express:
  - ANG II type 1 receptors
  - platelet-derived growth factor receptor-β
  - desmin
  - α-smooth muscle actin
  - VEGF receptor

- but do not express:
  - adipocyte marker S100
  - endothelial marker CD31

**Serum from TSC AML patients has increased:**

- VEGF-A
- VEGF-D
- soluble VEGF receptor 2 collagen type IV

*Siroky BJ et al Am J Physiol Renal Physiol. 2014*
SIZE OF AML vs AGE

Cox et al 2012
RATE OF AML GROWTH vs AGE

Cox et al 2012
Clinical presentation of AML

- Often discovered as an incidental finding on radiological studies
- Classical triad of presenting signs
  1. flank pain
  2. palpable mass
  3. haematuria

Clinical manifestations of AMLs

- Acute abdominal pain
- Chronic abdominal pain
- Acute flank pain
- Chronic flank pain
- Nausea and vomiting
- Fever
- Shock
- Hypertension
- Tenderness
- Palpable abdominal mass
- Palpable flank mass
- Anaemia
- Renal failure
- Microscopic haematuria
- Gross haematuria
- Urinary tract infection
- Haemorrhage

Bissler JJ, Kingswood JC. Kidney Int. 2004; 66(3):924-34
AMLs in Patients With TSC

- Cumulative risk of hemorrhage is 18% for women and 8% for men
  - Embolisation/nephrectomy in 25% to 50% of patients
  - Re-embolisation in up to 45% of patients
  - Risk of hemorrhage depends on size of AML (>3cm)

- Encroachment of AMLs on normal tissue may lead to renal failure

Song et al CMRO 2017
Encroachment??
Renal Cell Carcinoma in Patients With TSC

- Patients with TSC are at increased risk (\(?\)) (estimated 1%-3%) of developing renal cell cancer
- Histology is quite varied and usually low grade
- Disease develops at an earlier age: 30 versus 50 to 60 years, and primarily in women
- Especially fat-poor AML sometimes difficult to distinguish in MRI scan: experienced radiologist ± tumor biopsy

Bissler and Kingswood 2016
244 TSC patients with AML (1990-2012):

- 7 dialysis
- 7 transplantation
- 4 death with ESRD

ESRD: 18/244 = 7.3%
Natural history in TSC-AML

- 605 patients were selected (<18 years N.225; 18 years N.380)
- CKD occurred in 12.4% of patients <18 ys (CGS) and 23.4% of patients >18 ys
- Some functional CKD to occur in almost all patients within 6 years of diagnosis.

Song et al CMRO 2017
Prevalence of CKD in the overall TSC population by age compared with the general UK population

Kingswood et al 2014
What is the cause of CKD in Patients With TSC

- CGS \textit{PKD1-TSC2}
- Loss of renal parenchyma due to \textit{embolizations or nephrectomies}
- \textit{Encroachment} of renal parenchyma by AML
- Glomerulocystic kidney disease?

- Somatic \textit{second-hit} mutations occurring during rapid cell division (when the kidney still has growth and repair potential at age <35–40) may cause an accelerated \textit{loss of normal renal tissue} leading to CKD.
- \textit{TSC1} or \textit{TSC2} haploinsufficiency may lead to modest \textit{mTORC1 overactivity} and, therefore, glomerular hypertrophy and hyperfiltration
- Either \textit{haploinsufficiency or second} hit in the tubule cells could predispose to premature apoptosis or maldifferentiation

\textit{Kingswood et al Nephron 2016}
AML Treatment

- There have not been any controlled trials of embolization, nor any trials to compare treatment modalities (surgery, embolization & mTOR inhibitor treatment).
- Embolization 32% recurrence
- Risk for bleeding should be treated
  - Once a diameter of 3-4 cm is reached, complications may develop in 68–80% of patients

- Surgery and embolization should be performed as emergency treatment in bleeding episodes
- AML treatment with mTOR inhibitors should be initiated in all elective treatment situations

Kingswood et al 2016
Treatment decision

• Acute bleeding:
  – Embolization
    • Partial nephrectomy if not available
      – Total nephrectomy if not feasible

• Asymptomatic AML
  – <3cm diameter: follow up
  – >3cm diameter: propose treatment (pros and cons)

Kingswood et al 2016
Kingswood et al 2016
# Sirolimus in TSC-AML

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
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</tr>
<tr>
<td></td>
<td>( n = 20 )</td>
<td>( n = 16 )</td>
<td>( n = 36 )</td>
<td>( n = 17 )</td>
</tr>
<tr>
<td></td>
<td>6: TSC only</td>
<td>7: TSC only</td>
<td>15: TSC only</td>
<td>all TSC only</td>
</tr>
<tr>
<td></td>
<td>8: TSC + LAM</td>
<td>3: TSC + LAM</td>
<td>21: TSC + LAM</td>
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<tr>
<td></td>
<td>6: sporadic LAM</td>
<td>6: sporadic LAM</td>
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<td><strong>Inclusion criterion</strong></td>
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<tr>
<td></td>
<td>( \geq 1 \text{ AML} \geq 1 \text{ cm} )</td>
<td>( \geq 1 \text{ AML} \geq 2 \text{ cm} )</td>
<td>( \geq 1 \text{ AML} \geq 2 \text{ cm} )</td>
<td>( \geq 1 \text{ AML} &gt; 2 \text{ cm} )</td>
</tr>
<tr>
<td><strong>Maintenance sirolimus troughlevel (ng/mL)</strong></td>
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<tr>
<td></td>
<td>1–5 in 1</td>
<td>3–6 in 12</td>
<td>3–15</td>
<td>4–8</td>
</tr>
<tr>
<td></td>
<td>10–15 in 19</td>
<td>6–10 in 4</td>
<td></td>
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<tr>
<td><strong>End point</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Total AMLs volume (MRI)</td>
<td>Total AMLs size(^a) (MRI)</td>
<td>Total AMLs size(^a) (MRI)</td>
<td>Volume of the largest AML (MRI)</td>
</tr>
<tr>
<td><strong>Mean decrease in AML volume/size at 12 months</strong></td>
<td></td>
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<tr>
<td></td>
<td>47% in volume</td>
<td>39% in size</td>
<td>30% in size</td>
<td>66% in volume</td>
</tr>
</tbody>
</table>

\(^a\)As defined by the sum of the longest diameters of all target AMLs.
EXIST-2

EXIST-2: Phase III, Multicenter, Placebo-Controlled Study in AML EVEROLIMUS

EXIST-2 design

N = 118 patients ≥18 years old
Diagnosis of TSC (per consensus criteria) or sLAM (proven by biopsy or chest CT)
≥1 renal angiomyolipoma lesion ≥3 cm in longest diameter using CT/MRI
No renal angiomyolipoma-related bleeding or embolization in past 6 months

Randomization

1. Placebo (n = 39)
2. Oral everolimus 10 mg once daily (n = 79)

Double-Blind Core Phase

Crossover allowed at renal AML progression

Core phase analysis (June 30, 2011)

Median duration, everolimus, 9.7 months placebo, 7.8 months

Open-Label Extension Phase

Oral everolimus 10 mg once daily

Unblinding took place before the extension phase

Median duration of everolimus 39.8 months

Est. completion date (LPLV) February 2015

~3.5-year analysis (April 1, 2014)
Long term effect of everolimus in AML

Everolimus (n = 101)

Decrease in best % change from baseline: 98 (97%)
Increase in best % change from baseline: 3 (3%)

MEDIAN: 47 months on everolimus

Bissler et al 2014
EXIST-2 EXTENSION: % reduction AML

Bissler et al PLOS one 2017
EXIST-2 EXTENSION: time to AML progression

16 progressors
- 10 experienced increase in kidney size
- 6 experienced increase in renal angiomyolipoma size

No. of patients at risk
112 100 99 96 96 96 92 91 91 91 89 83 81 81 80 63 62 54 52 52 48 33 21 17 16 11 3 1 0

Bissler et al PLOS one 2017
EXIST 2 CKD

N=112

Bissler et al 2014
EXIST-2: do everolimus plasma levels correlate with efficacy?

- EXIST-2: 10 mg per day. Only decrease because of AE. No modifications based on plasma levels.
- Percent change, rather than absolute change, from baseline in angiomyolipoma lesion volume was correlated with everolimus Cmin concentration
- For nephrologists: everolimus without plasma levels? PROBABLY NOT.
  - Suggested: 4-10 ng ml$^{-1}$
EXIST-2: Angiogenic biomarkers

Moderate decrease in sVEGFR2 level and lack of everolimus effect on sVEGFR1, c-Kit and PLGF levels supports the hypothesis that everolimus may, at least partially, act through an anti-angiogenic mechanism in these patients.

Budde et al Br J Pharmacol 2015
VEGF-D vs change of AML volume

EXIST2, week 24

Bissler et al 2013
## EXIST-2 EXTENSION: AEs

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>≤12 months N = 112</th>
<th>13–24 months n = 101</th>
<th>25–36 months n = 100</th>
<th>37–48 months n = 91</th>
<th>49–60 months n = 52</th>
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</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>46 (41.1)</td>
<td>9 (8.9)</td>
<td>5 (5.0)</td>
<td>5 (5.5)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>36 (32.1)</td>
<td>21 (20.8)</td>
<td>20 (20.0)</td>
<td>20 (22.0)</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Acne</td>
<td>28 (25.0)</td>
<td>8 (7.9)</td>
<td>6 (6.0)</td>
<td>2 (2.2)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (23.2)</td>
<td>11 (10.9)</td>
<td>6 (6.0)</td>
<td>4 (4.4)</td>
<td>1 (1.9)</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>25 (22.3)</td>
<td>13 (12.9)</td>
<td>11 (11.0)</td>
<td>7 (7.7)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Aphthous stomatitis</td>
<td>21 (18.8)</td>
<td>15 (14.9)</td>
<td>9 (9.0)</td>
<td>5 (5.5)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (17.0)</td>
<td>2 (2.0)</td>
<td>4 (4.0)</td>
<td>4 (4.4)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>18 (16.1)</td>
<td>4 (4.0)</td>
<td>4 (4.0)</td>
<td>3 (3.3)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 (15.2)</td>
<td>7 (6.9)</td>
<td>7 (7.0)</td>
<td>4 (4.4)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Mouth ulceration</td>
<td>17 (15.2)</td>
<td>6 (5.9)</td>
<td>5 (5.0)</td>
<td>2 (2.2)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (15.2)</td>
<td>5 (5.0)</td>
<td>2 (2.0)</td>
<td>3 (3.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Bissler et al* PLOS one 2017
EXIST-2 EXTENSION: AEs

- Stomatitis/mucositis/mouth ulceration (~ 50%)
- Hypercholesterolemia (20–40%)
- Hypertriglyceridemia (12–50%)
- Infections (40–70%)
- Hypophosphatemia (11%)
- Amenorrhea (13–38%)
- Hematologic abnormalities (microcytosis, leukopenia, neutropenia) (10–40%)
- Proteinuria/microalbuminuria (4–30%)
EXIST-2 EXTENSION: renal AEs

- eGFR declined if CKD was present at baseline
- What about proteinuria???
But microalbuminuria increases...

<table>
<thead>
<tr>
<th>Patients</th>
<th>baseline creatinine (mg/dL)/MDRD (mg/min/1.73m²)</th>
<th>24 month creatinine (mg/dL)/MDRD (mg/min/1.73m²)</th>
<th>baseline proteinuria$^1$ (mg/mmol)</th>
<th>24 month proteinuria$^1$ (mg/mmol)</th>
<th>baseline cholesterol/HDL/LDL (mmol/L)</th>
<th>24 month cholesterol/HDL/LDL (mmol/L)</th>
<th>baseline triglycerides (mmol/L)</th>
<th>24 month triglycerides (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.84/76</td>
<td>0.78/81</td>
<td>6.1</td>
<td>12.1</td>
<td>159/89/90</td>
<td>184/74/101</td>
<td>45</td>
<td>52</td>
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<tr>
<td>2</td>
<td>0.93&gt;90</td>
<td>0.95&gt;90</td>
<td>22.4</td>
<td>40.0$^5$</td>
<td>118/46/72</td>
<td>167/54/100</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>1.22&gt;74</td>
<td>1.22&gt;74</td>
<td>10.3</td>
<td>3.7</td>
<td>205/74/131</td>
<td>3</td>
<td>144</td>
<td></td>
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<tr>
<td>4</td>
<td>0.96&lt;71</td>
<td>0.97&lt;78</td>
<td>8.1</td>
<td>12.1</td>
<td>175/83/94</td>
<td>171/64/139</td>
<td>116</td>
<td>64</td>
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<tr>
<td>5</td>
<td>0.99&lt;78</td>
<td>0.97&lt;78</td>
<td>9.1</td>
<td>8.2</td>
<td>202/63/139</td>
<td>181/44/125$^4$</td>
<td>116</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>0.67&lt;90</td>
<td>0.58&lt;90</td>
<td>5.0</td>
<td>9.6</td>
<td>240/86/156</td>
<td>152/63/89$^4$</td>
<td>198</td>
<td>116</td>
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<tr>
<td>7</td>
<td>1.15&lt;60$^0$</td>
<td>0.98&lt;60</td>
<td>9.4</td>
<td>28.6$^5$</td>
<td>192/78/114</td>
<td>188/77/102</td>
<td>47</td>
<td>47</td>
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<tr>
<td>8</td>
<td>1.07&lt;83</td>
<td>1.09&lt;80</td>
<td>5.6</td>
<td>1.0</td>
<td>154/56/98</td>
<td>202/66/120</td>
<td>62</td>
<td>77</td>
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<tr>
<td>9</td>
<td>0.77&lt;90</td>
<td>0.86&lt;90</td>
<td>13.2</td>
<td>47.0$^5$</td>
<td>125/86/90</td>
<td>226/52/136$^4$</td>
<td>102</td>
<td>186</td>
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<tr>
<td>10</td>
<td>0.85&lt;78</td>
<td>0.77&lt;87</td>
<td>5.0</td>
<td>4.3</td>
<td>212/65/157</td>
<td>167/75/82$^4$</td>
<td>48</td>
<td>51</td>
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<tr>
<td>11</td>
<td>0.71&gt;50$^0$</td>
<td>0.86&lt;78</td>
<td>7.7</td>
<td>9.4</td>
<td>94/40/54</td>
<td>118/41/64</td>
<td>76</td>
<td>62</td>
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<tr>
<td>12</td>
<td>0.42&gt;90</td>
<td>0.46&gt;90</td>
<td>13.3</td>
<td>11.1</td>
<td>142/38/104</td>
<td>193/42/127</td>
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<td>120</td>
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<tr>
<td>13</td>
<td>0.62&lt;50</td>
<td>0.61&lt;90</td>
<td>6.6</td>
<td>9.8</td>
<td>163/66/87</td>
<td>164/84/90</td>
<td>53</td>
<td>41</td>
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<tr>
<td>14</td>
<td>0.83&gt;90</td>
<td>1.01&gt;90</td>
<td>9.4</td>
<td>8.9</td>
<td>203/83/120</td>
<td>176/39/104</td>
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<td>15</td>
<td>0.68&lt;90</td>
<td>0.69&lt;90</td>
<td>9.0</td>
<td>18.2</td>
<td>200/78/122</td>
<td>170/75/80</td>
<td>66</td>
<td>73</td>
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<tr>
<td>16</td>
<td>0.82&lt;90</td>
<td>0.84&lt;90</td>
<td>12.9</td>
<td>11.9</td>
<td>156/61/105</td>
<td>120/49/50$^4$</td>
<td>145</td>
<td>104</td>
</tr>
<tr>
<td>17</td>
<td>1.30&lt;42$^0$</td>
<td>1.24&lt;44</td>
<td>22.4</td>
<td>32.3$^5$</td>
<td>292/106/189</td>
<td>216/59/147$^4$</td>
<td>243</td>
<td>117</td>
</tr>
</tbody>
</table>

0-Patients 7, 11, 17 had undergone a nephrectomy at least one year before the start of the trial
1-Expressed as a protein-to-creatinine ratio
2-Patient 3 was withdrawn at 12 months of treatment due to nephrotic-range proteinuria that reverted after discontinuation of treatment.
3-Patient 4 was excluded at 10 months due to acute pyelonephritis and did not want to be rechallenged.
4-Statins were prescribed in patients 5, 6, 9, 10, 14, 16, 17
5-ACEI were prescribed for microalbuminuria in patients 2, 7, 9, 17

1 patient in EXIST-2 and one in Barcelona trial: **nephrotic range proteinuria**

Cabrera et al OJRD 2012
LONG TERM EFFECTS OF mTOR inh IN THE KIDNEY

• Podocitary expression of nephrin, TRPC6 and Nck are significantly decreased under long term mTOR inhibitors exposure.
• mTOR inhibitors reduce podocitary adhesion and motility.
• Long term effects on proteinuria and kidney function are unknown.
Then...

- Will mTOR inhibitors target several renal abnormalities in TSC kidneys

or

- Will they worsen the progression of CKD?
Everolimus for other TSC manifestations

Subependimal giant cell astrocytoma. EXIST-1

Epilepsy. EXIST-

LAM
Facial angiofibromas
<table>
<thead>
<tr>
<th>Newly diagnosed or suspected TSC</th>
<th>Diagnosed with definite or possible TSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surveillance of kidneys</strong></td>
<td>Obtain MRI of the abdomen to assess angiomyolipoma progression and renal cystic disease (every 1–3 years for life) Assess renal function (GFR and blood pressure) at least annually</td>
</tr>
<tr>
<td>Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts</td>
<td>Obtain MRI of the abdomen to assess angiomyolipoma progression and renal cystic disease (every 1–3 years for life) Assess renal function (GFR and blood pressure) at least annually</td>
</tr>
<tr>
<td>Screen for hypertension by obtaining accurate blood pressure</td>
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<tr>
<td>Evaluate renal function by determining GFR</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td><strong>Management recommendations for renal angiomyolipoma</strong></td>
<td>Embolization (followed by corticosteroids for 7 days to mitigate post-embolization syndrome) [3]. Embolization should be as selective as technically feasible to preserve renal parenchyma Avoid nephrectomy</td>
</tr>
<tr>
<td>Angiomyolipoma with acute hemorrhage</td>
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<tr>
<td>Asymptomatic, growing angiomyolipoma &gt;3 cm in diameter</td>
<td>First-line: mTOR inhibitor Second-line: selective embolization or kidney-sparing resection</td>
</tr>
</tbody>
</table>

Kingswood et al, Nephron 2016;134:51–58
Conclusions-future directions

- mTOR inhibitors: first choice for preemptive treatment of growing AML >3 cm in diameter
- Potential benefits of preventive therapy in reducing AML-related morbidities may outweigh the risks of long-term therapy
- Future studies should address the impact of early detection and appropriate treatment of renal AML on preserving renal function (before AML>3 cm?)
- Plasma angiogenic biomarkers as measure of treatment efficacy
- Future studies should address the impact of adverse events related to mTOR.
Thanks!!!
Next webinar: June 29, Claus Schmitt (Heidelberg)

Optimizing PD in Children