A Novel Therapeutic Strategy of ADPKD

Osaka University Graduate School of Medicine
Department of Nephrology
Yoshitaka Isaka
A Novel Therapeutic Strategy of ADPKD

EPIDEMIOLOGY OF ADPKD
ADPKD is the most common hereditary renal disorder. Under ADPKD, multiple renal cysts are progressively developed and enlarged in both kidneys. As the cysts increase and enlarge, the renal function progressively deteriorates.

Estimated number of ADPKD patients is approximately 31,000 in Japan. 85% of patients have abnormality in \textit{PKD1} gene (code for polycystin 1), and 15% of patients have abnormality in \textit{PKD2} gene (code for polycystin 2).
Primary disease in dialysis-initiated patients

- Source: The Japanese Society for Dialysis Therapy Website

The proportion of dialysis-initiated patients by ADPKD is almost constant at 2.5 - 3%
The exact number of dialysis-initiated patients by ADPKD is increasing, because total number of dialysis-initiated patients is increasing.
In 1994, dialysis patients by ADPKD were 4,594, and non-dialysis ADPKD patients were estimated approximately 10,000 by survey.

Number of ADPKD patients were estimated at 31,000, but there may be more patients.
Primary diseases of total dialysis patients are similar in Korea.

Total number of new dialysis patients is also increasing in Korea. The number of new dialysis patients by ADPKD is increasing.

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<td>1.8</td>
<td>1.9</td>
<td>1.5</td>
<td>1.7</td>
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<td>Renal tuberculosis</td>
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<td>Pyelo/interstitial nephritis</td>
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<td>0.7</td>
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<td>0.8</td>
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<td>0.6</td>
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<td>0.8</td>
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<tr>
<td>Drugs or nephrotoxic agents</td>
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<td>0.6</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
<td>0.2</td>
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<td>0.5</td>
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<td>Kidney tumor</td>
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<td>0.3</td>
<td>0.2</td>
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<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
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<tr>
<td>Other</td>
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<td>3.0</td>
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<td>5.9</td>
<td>6.0</td>
<td>5.8</td>
<td>5.1</td>
<td>6.8</td>
<td>6.1</td>
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<td>16.6</td>
<td>20.2</td>
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<td>17.8</td>
<td>17.5</td>
<td>17.6</td>
<td>15.3</td>
<td>11.4</td>
<td>12.1</td>
<td>12.3</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Causes calculated as a percentage of new dialysis patients for each year.
Is ADPKD patients increasing?

Recently, ADPKD has been found in abdominal ultrasonography of healthy examination.
CT or MRI is preferable for the diagnosis of ADPKD

Cluster-shaped cysts are frequently observed
Cell transformation takes place around the cysts in ADPKD.
Differential diagnosis between ADPKD and multiple simple cysts is not easy. No daughter cysts were observed around a big cysts.

Although genetic testing is not common now, it may be necessary for differential, definitive diagnosis or prognosis of ADPKD.
Tips in the treatment of ADPKD patients

ENLARGEMENT OF KIDNEY IN ADPKD PATIENTS
Age and renal function in ADPKD patients

Renal function is stable until the kidney volume has increased up to 4 to 6 times normal size.

After significant and irreversible damage occurs, GFR declines.

Renal size gradually increased, but GFR significantly decreased after 6 years.

GFR is maintained for several decades by compensatory glomerular hyperfiltration and tubule hypertrophy.

Existing treatments mainly focused on renal function, urinalysis findings or blood pressure control, but kidney size needs to be checked.

Chapman A B et al. CJASN 2012;7:479-486
Rate of renal function decline assumed by kidney volume and age

Increase in kidney volume at constant rate per patient (Deterioration of renal function)

Growth rate of htTKV
- <1.5% (class 1A)
- 1.5-3% (class 1B)
- 3-4.5% (class 1C)
- 4.5-6% (class 1D)
- ≥ 6% (class 1E)

Kidney volume increases at a constant rate for each patient

Renal function declines at a constant rate

Irazabal M V et al. JASN 2015;26:160-172
How to Measure Kidney Volume: This is a big deal!!

**Integral Calculus**
- Actual calculation method
- Require specific software (It costs a lot)

**Ellipsoid Method**
- Calculation is cumbersome
- Measurement error is easy to occur
- Anyone can calculate

\[ \text{Kidney volume} = \frac{\pi}{6} \times \text{length} \times \text{width} \times \text{depth} \]
Extract left and right kidneys automatically from **CT image** to calculate volume.
A Novel Therapeutic Strategy of ADPKD

ADH INVOLVEMENT IN ADPKD PATIENTS
Change in Mean age at dialysis-initiation

-Source: The Japanese Society for Dialysis Therapy Website-

**Mean age at dialysis-initiation by PKD is younger!**

Trends of aging is slower, compared with other diseases!
Conventional therapy did not delay the start of RRT in ADPKD patients over time in Europe.

Incidence of RRT for ADPKD from the ERA-EDTA Registry.
Age-distribution of dialysis-initiated patients in Japan

Half of dialysis-initiated patients by ADPKD is under 65ys.
Potential benefit of tolvaptan treatment in delaying RRT

If tolvaptan can delay the start of RRT by 5-10 yrs, it will be a benefit for patients as well as for society, because they can continue to work. In case of progressive patients, early treatment may be effective.
Role of cAMP in ADPKD

PC1 or PC2 on the primary cilia senses the urinary flow and signals. If PC1 or PC2 is abnormal, intracellular Ca$^{2+}$ level decreases. When Ca$^{2+}$ level drops, intracellular cAMP concentration increases.

cAMP is also elevated by vasopressin by binding V2R, which activates PKA, and promotes cell proliferation and transepithelial fluid secretion in cysts, resulting in the formation and enlargement of cysts.
V2R antagonist, OPC31260, inhibited the progression in PKD model

(a) Kidney sections from PCK rats treated with OPC31260 between 3–10 or 10–18 weeks of age, compared with untreated controls.

(b) Kidney sections from CD1/pcy mice treated with OPC31260 between 4–30 weeks or 15–30 weeks of age, compared with untreated controls. *, untreated control rat killed at 15 weeks of age.

TEMPO 3:4 Trial:
Tolvaptan Efficacy and Safety in Management of Polycystic Kidney Disease and its Outcomes

Phase 3, multicenter, double-blind, placebo-controlled, 3-year trial.

ADPKD patients. 18-50 ys, with Ccr>60ml/min, TKV>750 ml, were randomly assigned to receive tolvaptan or placebo.

Primary outcome; change in TKV (%)
TEMPO 3:4 Trial
Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume.

Effect of Tolvaptan on the Annual Slopes of Total Kidney Volume.

Change in Total Kidney Volume

Tolvaptan: 2.80%/year  P<0.0001
Placebo: 5.51%/year

Effect of Tolvaptan on the Annual Slopes of Kidney Function (eGFR)

Tolvaptan: -2.61 (mg/dL)⁻¹
Placebo: -3.81 (mg/dL)⁻¹

P<0.0001

Percentage change in TKV from baseline at 36 months

Tolvaptan (n=92)
Placebo (n=55)

Muto S et al., Clin Exp Nephrol., 19(5), 867-877, 2015
Change in eGFR from steady-state postdose baseline at 36 months in Japan

Tolvaptan (n=92)

Placebo (n=55)

* eGFR (mL/min/1.73 m²) = 194 × Cr^{-1.094} × Age^{-0.287} (female: × 0.739)

Muto S et al., Clin Exp Nephrol., 19(5), 867-877, 2015
The objective was to assess the disease-modifying effects of tolvaptan on TKV and eGFR from baseline over the combined duration of TEMPO 3:4 and TEMPO 4:4.

Off-treatment; 13-829 days (mean 81 days, median 37 days)
Disease modification effect

- Start of disease modifying drug
- No treatment
- Late treatment start
- Early treatment start
- Ideal situation
- Progression

Review
The need for prognosticators in rheumatoid arthritis. Biological and clinical markers: where are we now?
Smolen JS et al., Arthritis Research & Therapy, 10(3), 208, 2008

Tolvaptan is not a fundamental treatment for ADPKD, but may slow the progression of ADPKD.
Percentage change in TKV from TEMPO 3:4 baseline to TEMPO 4:4 at 24 months

The largest effect of tolvaptan on TKV volume occurred within first year.

No significant change was observed between early and delayed group.

<table>
<thead>
<tr>
<th></th>
<th>Early Tolvaptan N</th>
<th>Delayed Tolvaptan N</th>
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</thead>
<tbody>
<tr>
<td>TEMPO 3:4</td>
<td>555</td>
<td>331</td>
</tr>
<tr>
<td>TEMPO 4:4</td>
<td>554 555</td>
<td>312 313</td>
</tr>
<tr>
<td>0</td>
<td>552 499</td>
<td>312 289</td>
</tr>
<tr>
<td>12</td>
<td>535 287</td>
<td>287 267</td>
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<tr>
<td>24</td>
<td>505</td>
<td>267</td>
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</table>
Adjustment for covariates showed the effectiveness of early treatment on TKV.

Covariates; age, gender, gender visit interaction, eGFR, eGFR visit interaction and urine ACR
Change in eGFR from the TEMPO 3:4 baseline to TEMPO 4:4 at 24 months.

<table>
<thead>
<tr>
<th>Treatment Duration (month)</th>
<th>Change in eGFR (mL/min/1.73m²)</th>
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<tbody>
<tr>
<td>Early Tolvaptan N</td>
<td>555</td>
</tr>
<tr>
<td>Delayed Tolvaptan N</td>
<td>331</td>
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<tr>
<td>Early Tolvaptan - Follow-up</td>
<td>553</td>
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<tr>
<td>Placebo - Follow-up</td>
<td>308</td>
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Discontinuation of tolvaptan induces increase of eGFR. eGFR is higher in early G.

**Tolvaptan induces initial decline in eGFR.**

No inferiority

<table>
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<tr>
<th>Treatment</th>
<th>N</th>
<th>eGFR Slope (mL/min/1.73m²/year)</th>
<th>Treatment Difference</th>
<th>95% CI</th>
<th>p-value</th>
<th>NI margin</th>
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<td>Early-Treated*</td>
<td>548</td>
<td>-3.26</td>
<td>-0.11</td>
<td>-0.75, 0.52</td>
<td>0.73</td>
<td>0.65</td>
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<td>Delayed-Treated*</td>
<td>304</td>
<td>-3.14</td>
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* p<0.05
** p<0.01
Change from baseline in TKV and eGFR by gender

**Male**
- Total Kidney Volume Growth (% of baseline)
- Change in eGFR (mL/min/1.73m²)

**Female**
- Total Kidney Volume Growth (% of baseline)
- Change in eGFR (mL/min/1.73m²)

Female shows the larger acute response to tolvaptan

No difference in eGFR decline by gender
Change from baseline in TKV and eGFR by CKD stage

**Effects of tolvaptan on TKV and eGFR were prominent in more severe groups**
Effects of tolvaptan on TKV and eGFR were prominent in more severe groups.
Effects of tolvaptan on TKV and eGFR were prominent in more severe groups.

Change from baseline in TKV and eGFR by imaging classification

Class 1B or 2A-B

Class 1C-1E

Total Kidney Volume Growth (% of baseline)

TEMPO 3:4

TEMPO 4:4

Early Tolvaptan N 56
Delayed Tolvaptan N 35

Early Tolvaptan N 56
Delayed Tolvaptan N 35

TEMPO 3:4

TEMPO 4:4

Early Tolvaptan n=56
Delayed Tolvaptan

Early Tolvaptan n=124
Delayed Tolvaptan

Change in eGFR (mL/min/1.73m²)

TEMPO 3:4

TEMPO 4:4

Early Tolvaptan n=56
Delayed Tolvaptan

Early Tolvaptan n=124
Delayed Tolvaptan

Early Tolvaptan n=494
Delayed Tolvaptan

Early Tolvaptan n=494
Delayed Tolvaptan

Effects of tolvaptan on TKV and eGFR were prominent in more severe groups.
Schematic design of the REPRISE clinical trial

**1st Endpoint**
Pre-treatment Off-Drug Baseline (Mean of 3 sCr)

**2nd Endpoint**
Pre-treatment slope from placebo run-in to post treatment follow-up

*SAP allowed for serum creatinine to be collected up to 40 days follow-up to complete the requirement for 3 samples*

### Clinical Characteristics at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tolvaptan Group (N=683)</th>
<th>Placebo Group (N=687)</th>
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<tbody>
<tr>
<td><strong>Age</strong> — yr</td>
<td>47.3 ±8.2</td>
<td>47.2 ±8.2</td>
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<tr>
<td><strong>Male sex</strong> — no. (%)</td>
<td>347 (50.8)</td>
<td>333 (48.5)</td>
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<tr>
<td><strong>Height</strong> — cm</td>
<td>174 ±10</td>
<td>173 ±10</td>
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<tr>
<td><strong>Weight</strong> — kg</td>
<td>84.6 ±19.9</td>
<td>81.6 ±19.3</td>
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<tr>
<td><strong>Body-mass index</strong></td>
<td>28.0 ±5.8</td>
<td>27.7 ±5.6</td>
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<tr>
<td><strong>Race</strong> — no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>626 (91.7)</td>
<td>632 (92.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>22 (3.2)</td>
<td>19 (2.8)</td>
</tr>
<tr>
<td>Black</td>
<td>25 (3.7)</td>
<td>23 (3.3)</td>
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<tr>
<td>Other</td>
<td>10 (1.5)</td>
<td>13 (1.9)</td>
</tr>
<tr>
<td><strong>Family history of polycystic kidney disease</strong> — no./total no. (%)</td>
<td>514/679 (75.7)</td>
<td>529/687 (77.0)</td>
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<td><strong>Blood pressure</strong> — mm Hg</td>
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<tr>
<td>Systolic</td>
<td>129.3 ±13.8</td>
<td>129.9 ±14.5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>82.1 ±9.6</td>
<td>82.6 ±9.7</td>
</tr>
<tr>
<td><strong>Estimated GFR</strong> — ml/min/1.73 m²‡</td>
<td>40.7 ±10.9</td>
<td>41.4 ±11.2</td>
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<tr>
<td><strong>Chronic kidney disease stage</strong> — no./total no. (%)</td>
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<tr>
<td>2</td>
<td>32/683 (4.7)</td>
<td>39/684 (5.7)</td>
</tr>
<tr>
<td>3a</td>
<td>209/683 (30.6)</td>
<td>202/684 (29.5)</td>
</tr>
<tr>
<td>3b</td>
<td>303/683 (44.4)</td>
<td>315/684 (46.1)</td>
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<td>4</td>
<td>139/683 (20.4)</td>
<td>128/684 (18.7)</td>
</tr>
<tr>
<td><strong>Hypertension</strong> — no. (%)§</td>
<td>634 (92.8)</td>
<td>640 (93.2)</td>
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<tr>
<td><strong>Current use of RAAS inhibitor</strong> — no. (%)</td>
<td>595 (87.1)</td>
<td>581 (84.6)</td>
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<tr>
<td><strong>History of kidney pain</strong> — no. (%)</td>
<td>338/675 (50.1)</td>
<td>344/679 (50.7)</td>
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<td><strong>Dose at end of single-blind tolvaptan period</strong> — no. (%)</td>
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<tr>
<td>60 mg in morning and 30 mg in afternoon</td>
<td>118 (17.3)</td>
<td>124 (18.0)</td>
</tr>
<tr>
<td>90 mg in morning and 30 mg in afternoon</td>
<td>565 (82.7)</td>
<td>563 (82.0)</td>
</tr>
</tbody>
</table>
Primary Endpoints: Change in eGFR

Tolvaptan Group (N=668) Placebo Group (N=663)

Annualized change in eGFR from baseline (mL/min/1.73 m² per year)

-2.34 -3.61

p <0.001

Dose at the end of double blind (12M)

Tolvaptan Group (n=578)
90/30mg: 60.6%
60/30mg: 29.9%
45/15mg, 以下: 9.5%

Placebo Group (n=637)
90/30mg: 70.2%
60/30mg: 26.8%
45/15mg, 以下: 3.0%

## Sub-group analysis of the primary endpoint

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Tolvaptan</th>
<th>Placebo</th>
<th>Mean eGFR Change (95%CI)</th>
<th>Tolvaptan</th>
<th>Placebo</th>
<th>Difference</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>668</td>
<td>663</td>
<td>-2.34 -3.61</td>
<td>1.27</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>≤55 yr</td>
<td>572</td>
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<td>White</td>
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<td>≤45 mL/分/1.73 m²</td>
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<td>-3.45 -4.35</td>
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<td>&gt;45 mL/分/1.73 m²</td>
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<td>-2.20 -4.11</td>
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Change in eGFR over Course of the Trial

During the tolvaptan run-in phase, GFR drop was observed.

Discontinuation increased GFR.

Difference in eGFR slope: 1.01 mL/min/1.73 m²/yr

Tolvaptan (n=680): -3.16
Placebo (n=682): -4.17

p<0.001

Tolvaptan slows the rate of eGFR decline and its effect is sustained

Annualized eGFR vs Follow-up Duration

Annualized eGFR Slope (mL/min/1.73m²/year)

From Mo1 to last follow-up (years)

Algorithm of tolvaptan treatment in ADPKD

Renal cysts
- Confirm ADPKD diagnosis

Typical ADPKD
(Bilateral/diffuse cyst distribution)
- Measure total kidney volume by CT/MRI
- Mayo Class 1C, 1D or 1E
- Rapidly progressive ADPKD
  - eGFR ≥ 25 ml/min
  - Age: 18-55
- Recommend starting tolvaptan
- Reassurance/Confirm rate of progression in 2-3 years

Atypical ADPKD
(focal disease or parenchymal atrophy)
- Monitoring

General management of ADPKD
- Blood pressure control
- Moderate sodium restriction
- Increased hydration
- Maintain normal BMI
- Cholesterol: LDL < 100, HDL > 50 mg/dL
- Moderate protein and phosphorus restriction
- Maintain serum bicarbonate ≥ 22 mEq/L

Time to First Elevation of ALT Level (3 times > normal range)

Hazard ratio, 4.91 (95% CI, 2.29-10.53)

Proportion of Patients with Alanine Aminotransferase Level > 3 × ULN

Days since Randomization

Tolvaptan

Placebo

Algorithm of potential drug-induced liver injury

**AST, ALT, bilirubin Increased to ≥ 3 X**

**AST, ALT, bilirubin Increased to > 2 X Or > 2 X baseline**

**Multiple signs and symptoms highly suggestive of liver injury**

**Hold tolvaptan**

**Repeat LFTs within 48-72 hr**

- **Increased to ≥ 3 X**
  - **Permanently discontinue tolvaptan unless other explanation for liver injury and injury resolved**
- **Stable or improved**
  - **Reinitiate tolvaptan with frequent monitoring**

**Assess for other etiologies (other disease, drugs, exposures)**

**Additional work-up and expert consultation if needed**

LFT, liver function tests.