TKV as a surrogate endpoint in ADPKD

How to determine clinically meaningful size-effect?

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Disclosure

• Dr. Vijay Modur is an employee of Sanofi
Surrogate Endpoint

- Section 507(e)(9) of the FD&C Act “[t]he term ‘surrogate endpoint’ means a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is not itself a direct measurement of clinical benefit, and—

- “(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or

- “(B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product in accordance with section 506(c).”

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure
Reasonably likely surrogate endpoint

• *Reasonably likely SEs* are, as the name suggests, reasonably likely to predict a clinical benefit. These SEs are supported by strong mechanistic and/or epidemiologic rationale, but the amount of clinical data available is not sufficient to show that they are validated. They can be used to support accelerated approval, but post-approval clinical trials are needed to show that these SEs can be relied upon to predict, or correlate with, clinical benefit.

Key challenge for a novel surrogate endpoint

• How to estimate effect-size of surrogate endpoint for clinical benefit to enable design of a trial?
Background

- ADPKD is a hereditary disease (~1 in 1,000 individuals) caused by PKD1 or 2 mutations characterized by cyst formation and massive kidney enlargement
  - In early stages of disease, growth in kidney size does not significantly impact renal function
  - Continued increase in cyst volume leads to destruction of nephrons and eventually to renal failure

Main endpoints in ADPKD

- Total Kidney Volume (TKV)
  - Well documented progression, reduced variability
  - Surrogate endpoint suitable for accelerated approval (US)
- Renal function (ESRD)
  - Ultimate clinical outcome in ADPKD, but very long timeline renders it not feasible for a clinical trial
  - Need for surrogate endpoints
  - eGFR slope is an accepted surrogate endpoint for ESRD
Mechanistic rationale for TKV

- Cyst formation and growth leads to disease
- Total cyst volume is highly correlated with Total Kidney Volume (TKV)
- TKV growth precedes renal function decline
PKD mutation causes cyst formation and growth

- Changes in gene expression
  - Increased proliferation and secretion
- Kidneys slowly replaced by multiple cysts
- Cyst formation and growth
- Mitotic orientation defects
- Transcriptional misregulation

PKD mutation
High correlation between total cyst volume and TKV

Table 2. Pearson correlations at each visit time point

<table>
<thead>
<tr>
<th>Visit</th>
<th>lnhtTKV versus lnhtTCV</th>
<th>lnhtTKV versus lnhtTCN</th>
<th>lnhtTCN versus lnhtTCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.93</td>
<td>0.80</td>
<td>0.85</td>
</tr>
<tr>
<td>1</td>
<td>0.94</td>
<td>0.83</td>
<td>0.87</td>
</tr>
<tr>
<td>2</td>
<td>0.93</td>
<td>0.81</td>
<td>0.88</td>
</tr>
<tr>
<td>3</td>
<td>0.94</td>
<td>0.83</td>
<td>0.88</td>
</tr>
<tr>
<td>6</td>
<td>0.95</td>
<td>0.78</td>
<td>0.83</td>
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<tr>
<td>8</td>
<td>0.97</td>
<td>0.86</td>
<td>0.90</td>
</tr>
<tr>
<td>10</td>
<td>0.95</td>
<td>0.80</td>
<td>0.87</td>
</tr>
<tr>
<td>12</td>
<td>0.97</td>
<td>0.80</td>
<td>0.84</td>
</tr>
</tbody>
</table>

All correlations were significant at \( P<0.001 \). lnhtTKV, log transformed height-adjusted total kidney volume; lnhtTCV, log transformed height-adjusted total cyst volume; lnhtTCN, log transformed height-adjusted total cyst number.
TKV growth precedes loss of renal function

Average standardized change in htTKV and GFR (n=93).

P=0.01 based on paired t test comparing each year to baseline for htTKV (*) and GFR (#). htTKV, height-adjusted total kidney volume.

Data from CRISP cohort

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Renal Insufficiency in ADPKD, Chapman et al.
Epidemiologic rationale

• Patients with higher TKV have lower renal function
• Patients with higher TKV for age have a more rapid progression
• Rate of increase in TKV is correlated to rate of decline in renal function

• How can we use this information to estimate a size-effect for clinically significant change in TKV?
ADPKD patients: Total Kidney Volume (TKV) correlates with renal function loss

Baseline hTKV of >600 mL is associated with a high risk of progression to stage 3 CKD within 8 years.
Imaging Classification of Autosomal Dominant Polycystic Kidney Disease: A Simple Model for Selecting Patients for Clinical Trials

**Mayo Model**


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**Link to article**
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Growth rate of TKV is associated with rate of renal progression

Imaging Classification based on height-adjusted TKV (HtTKV) relative to age

- Patient with HtTKV = 600 at age 20 => Class 1E
- Patient with HtTKV = 600 at age 27 => Class 1D
- Patient with HtTKV = 600 at age 40 => Class 1C
- Patient with HtTKV = 600 at age 60 => Class 1B


Confirmation of Mayo Model

• Analysis of two prospective, longitudinal studies:

  • Consortium of Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP*) study
    • Prospective, longitudinal study in 241 ADPKD patients with a creatinine clearance of at least 70 ml/min

  • HALT-PKD* study
    • Randomized clinical study that evaluated the effect of rigorous versus standard blood pressure control on rate of TKV growth and eGFR decline in 558 ADPKD patients with baseline eGFR > 30 mL/min/1.73m²

• Individual TKV growth rate and eGFR rate of decline estimated for each patient from longitudinal assessments:
  • Average longitudinal follow-up: 6.5 years
  • Average number of measurements per patient:
    • 4 measurements of TKV
    • 10 measurements of eGFR

*NCT Numbers: NCT01039987, NCT00283686, and NCT01885559
Flowchart of study population included in the analysis

CRISP
N = 241

HALT-PKD
N = 558

Patients excluded

CRISP
N = 237

HALT-PKD
N = 485

Patients included
N=722
1A: 44, 1B: 165, 1C: 251, 1D: 167, 1E: 95

No post-baseline TKV or eGFR (n=4)

No baseline height, TKV or GFR (n=18)
No post-baseline TKV or eGFR (n=55)
Relationship between TKV growth and eGFR decline in CRISP and HALT-PKD studies

Class 1A to 1E show increasing rate of progression for both TKV and eGFR

Population in STAGED-PKD: 1C to 1E

Based on retrospective analysis of two historical studies (CRISP and HALT-PKD) performed by sanofi
For each class, TKV growth rate is plotted against eGFR rate of decline. The size of each bubble is proportional to the sample size.
Significant correlation between TKV growth and eGFR decline

<table>
<thead>
<tr>
<th>TKV growth rate (%/year)</th>
<th>Predicted eGFR rate of decline (ml/min/1.73m²/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4%</td>
<td>2.46</td>
</tr>
<tr>
<td>5%</td>
<td>2.71</td>
</tr>
<tr>
<td>6%</td>
<td>2.96</td>
</tr>
<tr>
<td>7%</td>
<td>3.21</td>
</tr>
<tr>
<td>8%</td>
<td>3.46</td>
</tr>
<tr>
<td>9%</td>
<td>3.72</td>
</tr>
<tr>
<td>10%</td>
<td>3.97</td>
</tr>
</tbody>
</table>

Reducing TKV growth rate from 8%/year to 4%/year (50% reduction) would reduce eGFR rate of decline from 3.46 to 2.46 per year

⇒ 29% reduction (95% CI from 23% to 35%)

Predicted eGFR rate of decline based on a model predicting eGFR at time \( t \) as a function of TKV growth rate, and adjusted on baseline eGFR and age.
Meta-analysis of randomized clinical trials: Treatment effect on TKV vs. treatment effect on eGFR

- Meta-analysis including eligible trials:
  - Randomized, interventional trial (active vs. control)
  - At least 2 years of follow-up
  - Both TKV growth rate and GFR rate of decline available
  - No confounding factor of acute kidney injury associated with study drug (*)

- Studies included in the meta-analysis:
  - HALT-PKD (low BP vs. standard BP)
  - TEMPO 3:4 (tolvaptan vs. placebo)
  - ALADIN (Octreotide vs. placebo)
  - DIPAK1 (Lanreotide vs. placebo)

- Method:
  - Meta-analysis stratified by Mayo class (when results by Mayo class available)
  - Analysis of the relationship between relative reduction in TKV growth rate and relative reduction in GFR rate of decline (Weighted estimates calculated)

(*) Everolimus study was excluded due to publication suggesting that everolimus is associated with acute kidney injury, with increasing risk with lower baseline eGFR (Ha et. al. BMC Cancer 2014, 14:906)
## TKV and GFR in selected studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Mayo class</th>
<th>Number of patients</th>
<th>TKV growth rate (%/year)</th>
<th>eGFR rate of decline (ml/min/1.73m²/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active</td>
<td>Control</td>
</tr>
<tr>
<td>HALT-PKD¹</td>
<td>1C</td>
<td>102</td>
<td>86</td>
<td>6.04</td>
</tr>
<tr>
<td></td>
<td>1D</td>
<td>51</td>
<td>71</td>
<td>5.89</td>
</tr>
<tr>
<td></td>
<td>1E</td>
<td>31</td>
<td>34</td>
<td>7.27</td>
</tr>
<tr>
<td>TEMPO 3:4²</td>
<td>1C</td>
<td>340</td>
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<td>161</td>
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<tr>
<td></td>
<td>1E</td>
<td>179</td>
<td>82</td>
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<tr>
<td>ALADIN³</td>
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<td>40</td>
<td>39</td>
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<tr>
<td>DIPAK1⁴</td>
<td>NA</td>
<td>153</td>
<td>152</td>
<td>4.15</td>
</tr>
</tbody>
</table>

1 Irazabal et al. Nephrol Dial Transplant (2016)  
3 Caroli et al. Lancet (2013)  
4 Meijer et al. JAMA (2018)
Relationship between reduction in TKV growth rate and reduction in GFR rate of decline

Square represents a single trial for a selected Mayo class, with % reduction in TKV growth rate plotted against % reduction in GFR rate of decline. Size of each square is proportional to the sample size. Vertical lines above and below correspond to 95% confidence intervals. Regression line (which is forced to pass through the origin) represents weighted reduction in GFR rate of decline for a given reduction in TKV growth rate. Dotted lines represent 95% CI of the regression line.

50% reduction in TKV growth rate predicted to be associated with 27% reduction in GFR rate of decline

p=0.0004
Conclusions

Multiple lines of evidence for TKV as a surrogate endpoint

• Mechanistic
  • Cyst is the disease
  • TKV is a measurement of total cyst burden in kidney
  • TKV growth precedes renal function decline
  • TKV correlates with renal function status

• Epidemiologic from well conducted studies
  • Disease progression is tied to TKV growth
  • Preliminary retrospective evidence shows correlation between reduction in TKV growth rate and reduction in rate of renal function decline

• Despite wealth of data, estimating clinically meaningful effect on a surrogate marker to design trials with novel therapies can be challenging
Acknowledgements

• Patients and their families

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