Pleiotropic effects of mTOR inhibitors: cardiovascular and cancer

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Why this topic?

• Since last year very little news in the immunosuppressive drug field:
  – No new drug in maintenance

• It’s time to assess the qualities and risks of existing drugs:
  – We now have sufficient experience and hindsight to do so
Mechanisms of action of immunosuppressants
Signal 3 is provided by stimulation of the mTOR pathway by IL2 and other cytokines.

- PI-3K / Akt pathway signalling influences T-cell proliferation, expansion and migration^{1–3}
- The pathway also controls lymphocyte size and metabolic activity^{4,5}


IL2, interleukin-2; mTOR, mammalian target of rapamycin; PI-3K, phosphoinositide 3 kinase.
mTOR: An important role in several physiological processes

- **Effects of mTOR stimulation**
  - Translation
    - Used by CMV for replication
    - Potential antiviral effect
  - Proliferation
    - T cells
    - Immuno-suppression
    - Immuno-regulation
  - Angiogenesis
    - Endothelial cells
    - Reduce vascular remodelling and fibrosis
  - Malignancy
    - Anti-malignancy effects

- **Transplant-specific downstream effects of mTOR stimulation**

- **Effect of mTOR inhibition**
  - Renal cancer
  - Breast cancer
  - Tuberous sclerosis

mTOR, mammalian target of rapamycin.
What were the hopes when mTOR-inhibitors were launched?

• To be as effective as CNIs as immunosuppressants but with less nephrotoxicity

• To protect from “chronic allograft nephropathy” in the setting or organ transplantation

• To have antineoplastic effects

• To have an antiviral effect
CARDIOVASCULAR EFFECTS
CVD in kidney transplantation is a significant risk factor

CVD events continue to be a major cause of death with a functioning graft

CVD events are a significant contributor to posttransplant graft loss

Diabetes is a common PRETRANSPLANT finding and an increasing indication for kidney transplantation, but is a key risk factor for subsequent cardiovascular events

Immunosuppressive medication can be modified to reduce the risk of CVD

CVD, cardiovascular disease.

CVD continues to be a major cause of death with a functioning graft.

Data from the Australia and New Zealand Dialysis and Transplant registry; Pilmore H et al. Transplantation 2010;89:851–7.

CVD, cardiovascular disease.
Renal allograft impairment increases the risk of some CVD events (ALERT trial; placebo arm)

ALERT trial: 2102 adult KTR; > 6 months posttransplantation; CsA-based immunosuppresion; increased serum total cholesterol; 1st patient 1996; randomized to either placebo or fluvastatin therapy 40mg/d 2y then 80mg/d; follow-up > 5y.

***p<0.001.
CVD, cardiovascular disease;
MACE, major adverse cardiac event.

Graft loss increases the risk of some CVD events (ALERT trial; placebo arm)

CVD, cardiovascular disease; MACE, major adverse cardiac event.

*\( p < 0.02 \); **\( p < 0.005 \); ***\( p < 0.001 \).

Can mTOR inhibitors reduce cardiovascular risk? (1)

• Reduction in CNI-related complications
  – May improve renal function$^{1,2}$
  – Hypertension less frequent with mTORi therapy vs. CNI$^{3,4}$
  – Dyslipidaemia more frequent with mTORi therapy$^{1,5–7}$ but is dose dependent$^7$ and can be well managed with statins

CNI, calcineurin inhibitor; CV, cardiovascular; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; mTORi, mammalian target of rapamycin inhibitor; PWV, pulse wave velocity.

Can mTOR inhibitors reduce cardiovascular risk? (2)

• Potential cardioprotective effects of mTOR inhibitors:
  – Preliminary studies using surrogates of CV risk suggest that conversion to mTORi therapy may improve CV risk posttransplant\textsuperscript{8–10}
    \begin{itemize}
    \item LVH as assessed by LVMi
    \item Arterial stiffness as assessed by pulse wave velocity (PWV) index or augmentation index
    \end{itemize}
  – Animal data suggest that mTOR inhibitors may restrict atherosclerosis\textsuperscript{11}

CNI, calcineurin inhibitor; CV, cardiovascular; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; mTORi, mammalian target of rapamycin inhibitor; PWV, pulse wave velocity.

Presence of LVH is a strong determinant of risk of CVD

- LVH is detected in 74% of patients at start of dialysis
- LVH in the 5th year after transplant predicted death (RR 2.15)

CVD, cardiovascular disease; LVH, left ventricular hypertrophy; RR, relative risk.

Everolimus for regression of left ventricular hypertrophy (1)

- 30 non diabetic *de novo* KT patients:

21 men, age 28-65 years) were randomized 1:2 ratio to EVR plus reduced exposure to CsA *vs.* standard exposure to CsA + MMF (steroids for all)

**Everolimus for regression of left ventricular hypertrophy (2)**

Average behavior of left ventricular mass index (LVMi) in KTRs receiving everolimus (EVL) ([Black Square]) and KTR controls ([white square]) during a 1-year observation period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVL therapy</td>
<td>7.825</td>
</tr>
<tr>
<td>Baseline LVMi (g/m²)</td>
<td>-0.339</td>
</tr>
</tbody>
</table>

Predictors of 1 yr changes in LVMi for 10 RTRs administered EVL and for 20 controls, by multivariate analysis

Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients

Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients: baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th></th>
<th>Cyclosporine</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 17)</td>
<td>3 yr (n = 15)</td>
<td>Baseline (n = 27)</td>
<td>3 yr (n = 24)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61 (33–74)</td>
<td>64 (36–77)</td>
<td>58 (28–78)</td>
<td>61 (31–81)</td>
<td>0.62&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>59</td>
<td>53</td>
<td>70</td>
<td>67</td>
<td>0.24&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>140 ± 14</td>
<td>134 ± 12</td>
<td>142 ± 15</td>
<td>136 ± 13</td>
<td>0.96</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>79 ± 11</td>
<td>71 ± 8**</td>
<td>77 ± 8</td>
<td>75 ± 10</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 4.0</td>
<td>26.6 ± 4.8**</td>
<td>26.6 ± 4.5</td>
<td>26.7 ± 4.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Number of antihypertensive drugs</td>
<td>1.4 ± 0.9</td>
<td>1.5 ± 1.0</td>
<td>2.1 ± 1.2</td>
<td>2.1 ± 1.3</td>
<td>0.97</td>
</tr>
<tr>
<td>BB</td>
<td>53%</td>
<td>53%</td>
<td>81%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>CCB</td>
<td>59%</td>
<td>53%</td>
<td>59%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>ACEI/AT2B</td>
<td>0%</td>
<td>20%</td>
<td>15%</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>18%</td>
<td>20%</td>
<td>33%</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0%</td>
<td>0%</td>
<td>26%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Statin users (%)</td>
<td>69</td>
<td>93</td>
<td>82</td>
<td>75</td>
<td>0.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>mGFR (mL/min/1.73 m²)</td>
<td>45 ± 11</td>
<td>52 ± 12**</td>
<td>50 ± 13</td>
<td>46 ± 13</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>119 ± 44</td>
<td>111 ± 41**</td>
<td>129 ± 38</td>
<td>134 ± 56</td>
<td>0.18</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.1 ± 1.5</td>
<td>13.2 ± 1.2**</td>
<td>11.9 ± 0.2</td>
<td>13.4 ± 1.4**</td>
<td>0.22</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.4 ± 1.6</td>
<td>5.5 ± 1.0*</td>
<td>6.3 ± 1.1</td>
<td>5.0 ± 0.9**</td>
<td>0.56</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.4 ± 0.3</td>
<td>1.8 ± 0.5**</td>
<td>1.4 ± 0.5</td>
<td>1.6 ± 0.7*</td>
<td>0.32</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.0 ± 1.3</td>
<td>3.0 ± 0.7**</td>
<td>4.0 ± 1.1</td>
<td>2.7 ± 0.7**</td>
<td>0.87</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.9 ± 0.9</td>
<td>1.7 ± 0.6</td>
<td>1.8 ± 1.1</td>
<td>1.5 ± 0.7*</td>
<td>0.58</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; BB, beta-blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; AT2B, angiotensin 2 blockers; mGFR, measured glomerular filtration rate; HDL, high-density lipoprotein, LDL, low-density lipoprotein.

<sup>a</sup>p-value derived from mixed model for difference between groups from baseline to three yr.

<sup>b</sup>p-value from independent Student t-test at baseline.

<sup>**</sup>p-value from independent Student t-test comparing change between baseline and three-year follow-up.

*p < 0.05 for intragroup change from baseline (mixed model).

**p < 0.01 for intragroup change from baseline (mixed model).

Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients

Graft survival is related to 1-year systolic blood pressure

Cadaver kidney recipients 1995–2000

Grafts surviving (%)

Time posttransplant (years)

**mTORi-based regimens may reduce hypertension**

<table>
<thead>
<tr>
<th>Study name / description</th>
<th>Study design</th>
<th>n</th>
<th>Parameter</th>
<th>Treatment group</th>
<th>Outcome</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Legendre et al 2003¹</td>
<td><em>De novo</em> sirolimus vs CsA</td>
<td>161</td>
<td>Hypertension (TE), %</td>
<td>Sirolimus</td>
<td>29.6</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CsA</td>
<td>47.5</td>
<td></td>
</tr>
<tr>
<td>Grinyo et al 2004²</td>
<td>Sirolimus with tacrolimus elimination vs sirolimus + tacrolimus</td>
<td>87</td>
<td>Mean blood pressure, mmHg</td>
<td>Sirolimus</td>
<td>132/75.6</td>
<td>0.03a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tacrolimus</td>
<td>141/80.4</td>
<td></td>
</tr>
<tr>
<td>Rapamune Maintenance Study³</td>
<td>Sirolimus with CsA elimination at month 3 vs sirolimus + CsA</td>
<td>430</td>
<td>Mean arterial pressure, mmHg</td>
<td>Sirolimus</td>
<td>97.1</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CsA</td>
<td>101.3</td>
<td></td>
</tr>
<tr>
<td>Baboolal 2003⁴</td>
<td>Sirolimus with CsA elimination at month 3 vs sirolimus + CsA</td>
<td>133</td>
<td>Hypertension as adverse event, %</td>
<td>Sirolimus</td>
<td>26.2</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CsA</td>
<td>40.0</td>
<td></td>
</tr>
<tr>
<td>Bertoni et al 2009⁵</td>
<td><em>De novo</em> CNI minimisation with everolimus vs CsA</td>
<td>106</td>
<td>Mean systolic blood pressure, mmHg</td>
<td>Everolimus</td>
<td>125</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CsA</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>A2309⁶</td>
<td><em>De novo</em> CNI minimisation with everolimus vs CsA</td>
<td>833</td>
<td>Hypertension as adverse event, %</td>
<td>Everolimus</td>
<td>29.6</td>
<td>_</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CsA</td>
<td>30.0</td>
<td></td>
</tr>
</tbody>
</table>

¹Diastolic only. CNI, calcineurin inhibitor; CsA, cyclosporin; mTORi, mammalian target of rapamycin inhibitor; ns, not significant; TE, treatment emergent.

• mTOR inhibitors:
  
  – Probably **reduce CV risk in transplant patients**: whether their use raises both graft and/or patient survival is debatable. The beneficial effect is probably true in specific high risk sub-groups.
ANTI NEOPLASTIC EFFECTS
Risk of cancer post-transplant 1965 to 31 March 2001
Primary CD & LD – ANZDATA Registry

JAMA, December 20, 2006—Vol 296, No. 23
Cancer risk following kidney transplantation

AUS + NZ
Risk factors associated with *de novo* cancer posttransplantation

- **Immunosuppression**
  - Duration
  - Intensity
  - Type

- **Exposure to UV light**
  - Total sun burden
  - Geographical region

- **Increasing recipient age**

- **Previous exposure to carcinogens**

- **History of malignancy**

- **General predisposition**

- **Chronic viral infection**
mTOR inhibitors may reduce the incidence of post-transplant *de novo* malignancies

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Transplants, n</th>
<th>De novo malignancies&lt;sup&gt;a&lt;/sup&gt;</th>
<th>De novo non-skin solid malignancies&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CsA / tacrolimus alone</td>
<td>30,424</td>
<td>552 1.81</td>
<td>304 1.00</td>
</tr>
<tr>
<td>Sirolimus / everolimus + CsA / tacrolimus&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2321</td>
<td>14 0.60</td>
<td>11 0.47</td>
</tr>
<tr>
<td>Sirolimus / everolimus alone&lt;sup&gt;c&lt;/sup&gt;</td>
<td>504</td>
<td>3 0.60</td>
<td>0 0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Within 963 days of transplant; <sup>b</sup>p<0.0001 for *de novo* malignancies and p=0.0125 for *de novo* non-skin solid malignancies vs. CsA / tacrolimus alone; <sup>c</sup>p=0.041 for *de novo* malignancies and p=0.011 for *de novo* non-skin solid malignancies vs. CsA / tacrolimus alone

mTORi, mammalian target of rapamycin inhibitor; CNI, calcineurin inhibitor; CsA, ciclosporin

Sirolimus + CsA + Steroids

> 5 ng/mL 150-400 ng/mL

N=525

Patients with a history of malignancy within 5 years before transplantation, other than adequately treated BCC or SCC, were excluded.

SRL-CsA-ST n=215

Sirolimus* (> 5 ng/mL)
CsA (50-150 ng/mL)
Steroids

SRL-ST n=215

Sirolimus* (20-30 ng/mL ≤ 1 yr)
(15-25 ng/mL > 1 yr)

Steroids

Discontinued Before randomization n=95

CsA Stopped
(25% per week)

Sirolimus therapy in *de novo* KTx and *de novo* posttransplant malignancies (1)

**Analysis of any skin carcinoma.**
(A) Kaplan-Meier plot of time to first skin carcinoma.
(B) Cumulative number of skin carcinomas.

**RMR study: On-therapy**

**RMR study: ITT**
Sirolimus therapy in *de novo* KTx and *de novo* posttransplant malignancies (2)

Kaplan-Meier plots of time to **non-skin malignancies**.
(A) On-therapy.
(B) Intention-to-treat.
CONCEPT study

- Open label randomized prospective multicentric French study evaluating conversion from CsA to sirolimus 3 months after kidney transplantation

Transplantation (n = 235)

- Daclizumab + Mycophenolate mofetil + Ciclosporine + STÉROIDS
- MMF + SRL group (n = 95)
- MMF + CsA group (n = 97)

Sirolimus (SRL)

Ciclosporine (CsA)

- Non-randomization criteria at 3 months
  - Acute rejection
  - Creatinine clearance < 40 mL/mn
  - Proteinuria > 1 g/d
  - MMF dose < 1.5 g/d

Lebranchu et al. AJT, 2012
CONCEPT study: 60 Month Results

**Cancers**

- **SRL**: 6.3%
- **CsA**: 13.2%

Lebranchu Y et al. AJT, 2012
The CONVERT study: SRL conversion vs. CNI continuation

Pre-randomization:
• Steroids
• MMF or AZA
• CsA or Tacrolimus

Screening

2:1 Randomization

SRL conversion
• Day 1: Stop CNI; SRL, 12-20 mg x 1
• Day 2: SRL 4-8 mg/day
• Days 5-7: Adjust to 8-20 ng/mL
• MMF or AZA: Continue or stop
• Continue steroids

CNI continuation
• Continue CsA or TAC (can switch CsA ⇔ TAC)
• MMF or AZA: continue or stop
• Continue steroids

Routine follow-up per protocol

SRL target trough concentrations based on chromatographic methods

Schena et al. Transplantation 2009
Significantly lower malignancy rates with sirolimus at 18 months (CONVERT study)

<table>
<thead>
<tr>
<th></th>
<th>CNI (n = 555)</th>
<th>SRL (n = 275)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>7.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Skin</td>
<td>2.0</td>
<td>1.1</td>
</tr>
<tr>
<td>PTLD</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>All others</td>
<td>0.5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Schena et al. Transplantation 2009

\[ p < 0.001 \]
\[ p = 0.002 \]
\[ p = 0.555 \]
\[ p < 0.001 \]
mTORi and Kaposi sarcoma

Sirolimus for Kaposi’s Sarcoma in Renal-Transplant Recipients

Giovanni Stallone, M.D., Antonio Schena, M.D., Barbara Infante, M.D., Salvatore Di Paolo, M.D., Antonella Loverre, Ph.D., Giulio Maggio, M.D., Elena Ranieri, Ph.D., Loreto Gesualdo, M.D., Francesco Paolo Schena, M.D.,

Kaposi’s sarcoma lesions in patient receiving MMF, CsA and steroids

1 month post-conversion to sirolimus
Sirolimus conversion for Kaposi’s sarcoma in renal transplant recipients

Incidence per 100 000 person years (Inc) and standardized incidence ratios (SIR) taking account of age, gender and geographical region

<table>
<thead>
<tr>
<th>Cancer (ICD 10)</th>
<th>Without mTORi n = 73 867</th>
<th>With mTORi n = 42 79</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Inc</td>
<td>SIR</td>
</tr>
<tr>
<td>Lip, oral cavity and pharynx (C00–14)</td>
<td>136</td>
<td>41</td>
<td>1.4</td>
</tr>
<tr>
<td>Digestive organs (C15–26)</td>
<td>593</td>
<td>179</td>
<td>1.0</td>
</tr>
<tr>
<td>Colorectum (C18–21)</td>
<td>270</td>
<td>82</td>
<td>0.9</td>
</tr>
<tr>
<td>Respiratory and intrathor. organs (C30–39)</td>
<td>504</td>
<td>152</td>
<td>1.2</td>
</tr>
<tr>
<td>Lung (C33)</td>
<td>452</td>
<td>136</td>
<td>1.3</td>
</tr>
<tr>
<td>Melanoma of skin (C43)</td>
<td>161</td>
<td>49</td>
<td>2.4</td>
</tr>
<tr>
<td>Non-melanoma skin (C44)</td>
<td>3231</td>
<td>1007</td>
<td>6.1</td>
</tr>
<tr>
<td>Mesothelial and soft tissue (C45–49)</td>
<td>147</td>
<td>44</td>
<td>5.2</td>
</tr>
<tr>
<td>Kaposi sarcoma (C46)</td>
<td>113</td>
<td>34</td>
<td>35.9</td>
</tr>
<tr>
<td>Breast, female patients (C50)</td>
<td>224</td>
<td>177</td>
<td>1.0</td>
</tr>
<tr>
<td>Female genital organs (C51–58)</td>
<td>169</td>
<td>133</td>
<td>1.4</td>
</tr>
<tr>
<td>Male genital organs (C60–63)</td>
<td>441</td>
<td>218</td>
<td>1.5</td>
</tr>
<tr>
<td>Prostate (C61)</td>
<td>405</td>
<td>200</td>
<td>1.5</td>
</tr>
<tr>
<td>Urinary tract (C64–68)</td>
<td>662</td>
<td>200</td>
<td>2.9</td>
</tr>
<tr>
<td>Kidney (C64–66)</td>
<td>513</td>
<td>155</td>
<td>6.9</td>
</tr>
<tr>
<td>Eye, brain, central nervous system (C69–72)</td>
<td>65</td>
<td>20</td>
<td>1.5</td>
</tr>
<tr>
<td>Thyroid, endocrine glands (C73–75)</td>
<td>82</td>
<td>25</td>
<td>4.3</td>
</tr>
<tr>
<td>Lymphoid, haematopoietic tissue (C81–96)</td>
<td>540</td>
<td>163</td>
<td>3.5</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (C82–85)</td>
<td>437</td>
<td>132</td>
<td>6.1</td>
</tr>
<tr>
<td>All cancers without non-melanoma skin</td>
<td>3756</td>
<td>1158</td>
<td>1.7</td>
</tr>
</tbody>
</table>

P-values for significance between SIR with or without mammalian target of rapamycin inhibitor (mTORi). Significant P value is shown in bold.
Immunosuppression with m-TOR inhibitor and incidence of post-transplant cancer in kidney transplant recipients

Opelz et al. Nephrol Dial Transplant (2016) 0: 1–8
Immunosuppression with m-TOR inhibitor and incidence of post-transplant cancer in kidney transplant recipients

Opelz et al. Nephrol Dial Transplant (2016) 0: 1–8
Immunosuppressive balance and risk of cancer

- **Infection**
  - HCV (HCC)
  - HPV (Skin cancer)
  - EBV (PTLD)

- **Immune System**
  - All immunosuppressive drugs

- **Angiogenesis**

- **Tumor Cell Growth**

- **Metastasis**

- **Cancer**

- **Cancer-Free**

- **Malignancy**
In conclusion

• mTOR inhibitors:
  
  – Reduce non-melanoma skin cancer risk in transplant patients especially *basocellular carcinomas*, probably not solid cancer risk.
  
  – This action needs to be proven against tacrolimus based IS.
THANK YOU