Mammalian Target of Rapamycin Inhibitors in Kidney Transplant Recipients: A CLUE in the Search for Skin Cancer Reduction after Transplant?

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LEARNING OBJECTIVES

1. Discuss the risk of malignancy post-transplantation
2. Explain the etiology of immunosuppression-related, post-transplant skin cancer
3. Describe the role of mammalian target of rapamycin (mTOR) and mTOR inhibitors (mTORIs) in skin cancer
4. Summarize currently available evidence regarding mTORI use in immunosuppressive regimens to reduce skin cancer risk in kidney transplant recipients (KTRs)
SETTING THE SCENE: KIDNEY TRANSPLANTATION

I. Graft survival for all KTRs
   A. 1 year: > 90%
   B. 5 year: ≥ 70%
   C. 10 year: < 60%

II. Reasons for graft loss
   A. Primary non-function (~12%)
      1. Defined as permanent absence of kidney function beginning immediately post-transplant
   B. Loss of functioning graft (~45%)
      1. Cardiovascular (28-45%)
      2. Infection (15-27%)
      3. Malignancy (13-18%)
         i. KTRs 3 to 5 times more likely to develop cancer than general population
         ii. Most common are skin malignancies

   Figure 1: Causes of DWFG in KTRs

THE SUSPECT: SKIN CANCER AND KIDNEY TRANSPLANTATION

III. Nonmelanoma skin cancers (NMSC)
   A. Include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)
   B. General population
      1. Most common cancers in U.S.
         i. > 2 million new cases in 2010
      2. Ratio of BCC to SCC is 4-5:1
   C. Kidney transplant population
      1. Most common cancers post-transplantation
         i. Account for 95% of skin cancers in KTRs
      2. Ratio of BCC to SCC is reversed at 1:5
D. SCC in KTRs\textsuperscript{6,8-9,12-14}

1. Incidence increased by 65-fold compared with general population

2. Morbidity and mortality
   i. Increased incidence of metastatic disease in organ transplant recipients (OTRs)
      a. 8% versus (vs.) 0.5-5% in general population
   ii. More aggressive disease
      a. Greater tumor burden
      b. More aggressive tumor behavior
   iii. OTRs have collectively worse outcomes
      a. Mortality rate of approximately 5%
      b. SCC accounts for > 60% of deaths from all skin malignancies in OTRs
      c. Designated as “high risk” tumors in immunosuppressed patients per the National Comprehensive Cancer Network\textsuperscript{®} (NCCN)
   iv. High risk for recurrence in KTRs
      a. After 1\textsuperscript{st} SCC, multiple subsequent skin cancers develop in 60-80% within 3 years (yr)

E. BCC in KTRs\textsuperscript{6,8,9}

1. Incidence increased by 10-fold compared with general population

2. Morbidity and mortality
   i. Characteristically indolent
   ii. Designated as “high risk” tumors in immunosuppressed patients per NCCN\textsuperscript{®}
   iii. Little data to suggest higher incidence of recurrence or progression to metastatic disease

F. Time to development of NMSC\textsuperscript{12,13}

1. Average onset 3 to 5 yr after transplantation
   i. Premalignant or malignant skin tumors develop in 40% of OTRs within 5 yr

G. Risk factors for skin cancer in OTRs

1. Exposure to ultraviolet (UV) light\textsuperscript{6-7,9,13,15-16} (Figure 2)
   i. Residence in high sun-exposure climates
   ii. History of chronic sun exposure and/or sun burns

2. Fitzpatrick skin type I-III\textsuperscript{8,9,13} (Table 1)

<table>
<thead>
<tr>
<th>SPT</th>
<th>Basic Skin Color</th>
<th>Response to Sun Exposure</th>
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<tbody>
<tr>
<td>I</td>
<td>Pale white</td>
<td>Do not tan, burn easily</td>
</tr>
<tr>
<td>II</td>
<td>White</td>
<td>Tan with difficulty, burn easily</td>
</tr>
<tr>
<td>III</td>
<td>White</td>
<td>Tan easily but may burn initially</td>
</tr>
<tr>
<td>IV</td>
<td>Light brown/olive</td>
<td>Tan easily, hardly burn</td>
</tr>
<tr>
<td>V</td>
<td>Brown</td>
<td>Tan easily, usually do not burn</td>
</tr>
<tr>
<td>VI</td>
<td>Black</td>
<td>Become darker, do not burn</td>
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3. History of skin cancer\textsuperscript{8,13,15,16}

4. History of human papillomavirus infection\textsuperscript{13,16}

5. Older age\textsuperscript{6,8,13}

6. Immunosuppression (IS)\textsuperscript{6-8,10-11,16}
   i. Type
   ii. Duration (Figure 2)
   iii. Intensity

7. Type of organ transplant\textsuperscript{8}
   i. Heart/lung > kidney > liver

8. History of biologic therapy\textsuperscript{8,16}
   i. Most commonly induction therapy

9. CD4 lymphocytopenia\textsuperscript{13}
Figure 2: Cumulative incidence with 95% CI of skin cancer in KTRs\textsuperscript{11}

CA: all skin cancers; QU: Queensland; NL: the Netherlands

THE WEAPON: IMMUNOSUPPRESSION AND SKIN MALIGNANCY

IV. Immunosuppressive regimens\textsuperscript{15,18}

A. Consist of maintenance therapy with or without induction therapy
   1. Induction therapy: high level IS at time of transplantation (Table 2)
   2. Maintenance therapy (Table 3)
      i. Long-term therapy to prevent acute rejection and deterioration of graft function
      ii. Consist of calcineurin inhibitors (CNIs)± antiproliferatives (antimetabolites or mammalian target of rapamycin inhibitors) ± corticosteroids (CCS)
      iii. Regimens vary based on center-specific protocols

<table>
<thead>
<tr>
<th>Table 2. Induction Agents\textsuperscript{18}</th>
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<tr>
<td><strong>Class of Agent(s)</strong></td>
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<tr>
<td>Lymphocyte Depleting</td>
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<tr>
<td>Non-lymphocyte Depleting</td>
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<tr>
<td>Interleukin-2 receptor antagonist (IL-2RA)</td>
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<tr>
<th>Table 3. Maintenance Agents\textsuperscript{18}</th>
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<tr>
<td><strong>Class of Agent(s)</strong></td>
</tr>
<tr>
<td>Calcineurin Inhibitors (CNIs)</td>
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<td></td>
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<tr>
<td>Antimetabolites</td>
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<tr>
<td>Mammalian Target of Rapamycin Inhibitors (mTORIs)</td>
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<tr>
<td></td>
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<tr>
<td>Corticosteroids (CCS)</td>
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<tr>
<td>Selective Costimulation Blocker</td>
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B. Immunosuppression-related skin cancer
   1. IS-related skin cancer results from decreased immunosurveillance and drug-specific properties\textsuperscript{14}
   2. Incidence of skin cancer related to intensity, duration, and type of IS\textsuperscript{7-8,10,12,16}
      i. Higher risk of malignancy with more intensive IS regimens
         a. Increased incidence of cancers seen with increasing doses of immunosuppressants
         b. Higher incidence of malignancy with multi-drug regimens
            1) Quadruple therapy > triple therapy > dual therapy > monotherapy
         c. Increased incidence of skin cancer in setting of CD4 lymphocytopenia in KTRs
      ii. Duration of immunosuppression\textsuperscript{10,11,16}
         a. Gradual and cumulative increase in neoplasia in KTRs
      iii. Type of immunosuppression
         a. Induction therapy\textsuperscript{8,10,16}
            1) Associated with increased risk of skin cancers
            2) Lymphocyte depleting agents appear to increase risk to a greater extent compared with non-lymphocyte depleting agents
         b. CCS\textsuperscript{16,19}
            1) Controversy exists over propensity to elevate skin cancer risk
               i) Increased risk of NMSC in non-transplant recipients
               ii) Used in treatment regimens for certain cancers
               iii) Difficult to discern effect in combination with other immunosuppressants in OTRs
         c. CNIs\textsuperscript{10,12,20,21}
            1) Increase risk of skin cancer through multiple mechanisms (Figure 4)
            2) Most relevant class of immunosuppressive agents in terms of skin cancer tumor initiation and promotion
d. Antimetabolites
   1) AZA\textsuperscript{8,12,16}
      i) Increase risk of skin cancer through two mechanisms (Figure 4)
   2) MPA\textsuperscript{16}
      i) Association with development of malignancy is controversial
         a. Studies have shown similar or reduced cancer rates compared with AZA
         b. May have antiproliferative and anti-cancer effects

e. Selective costimulation blocker: belatacept\textsuperscript{22,23}
   1) Limited information about risk of skin cancer with use
   2) Use appears to elevate risk of skin cancer with incidence comparable to CNIs

\textbf{Figure 4: CNI and AZA known mechanisms of tumor initiation and promotion}

\textbf{THE RETALIATION: THE ROLE OF mTOR AND mTOR INHIBITION IN SKIN CANCER}

V. mTOR\textsuperscript{24,25}
   A. Protein kinase acting as the catalytic component of 2 distinct multiprotein complexes, mTORC1 and mTORC2 (Figure 5)
      1. mTORC1
         i. Rapamycin- and nutrient-sensitive multiprotein complex
            a. Growth factors and nutrients, mainly amino acids, positively and negatively regulate activity
            b. Actions inhibited by rapamycin
      2. mTORC2
         i. Growth-factor-sensitive but nutrient-insensitive complex
         ii. Rapamycin does not bind to mTORC2, also called "rapamycin-insensitive complex"
Initiation of UV-induced Cellular Damage

- Production of reactive oxygen species (ROS)
- Activation of cell surface receptors
- Initiation of downstream signaling cascade

AKT/mTOR Pathway Activation

- Activation of mTORC2
- Phosphorylation of AKT by signaling cascade and mTORC2
- Inhibition of TSC 1/2 complex & PRAS40 via phosphorylation by AKT

mTORC1 Activation

- Disinhibition of mTORC1 resulting from PRAS40 inhibition
- Disinhibition of Rheb resulting from TSC 1/2 complex inhibition
- Strong activation of mTORC1 by Rheb

Cellular Growth & Cell Survival

- Inhibition of 4E-BP1 via phosphorylation by mTORC1
- Disinhibition of mRNA translation and promotion of cell survival resulting from 4E-BP1 inhibition
- Activation of S6K via phosphorylation by mTORC1
- Enhanced mRNA translation and resistance to cellular apoptosis resulting from activation of S6K

*Figure 5: UV-induced cellular activation of AKT/mTOR complexes pathway*
VI. mTOR inhibitors

A. Mechanism of action
   1. Inhibit T and B lymphocyte proliferation by preventing activation of mTOR which then halts progression from the G₁ to the S phase of the cell cycle

B. Background
   1. Sirolimus
      i. Rapamune® FDA approval (1999): prophylaxis of organ rejection in patients ≥ 13 yr of age receiving a renal transplant
         a. Low- to moderate-immunologic risk: use initially with CsA and CCS
         b. High-immunologic risk: use in combination with CsA and CCS for 1st 12 mos following transplantation
      ii. Dosing
         a. Low- to moderate-immunologic risk
            1) In combination with CsA: 6 mg on day 1, followed by 2 mg daily
            2) Following CsA withdrawal: 2-4 mos post-transplant, withdraw CsA over 4-8 weeks (wk) and adjust SRL dose based on trough concentrations
         b. High-immunologic risk
            1) In combination with CsA: 15 mg on day 1, followed by 5 mg daily
      iii. Therapeutic drug monitoring
         a. Following CsA withdrawal in low- to moderate-immunologic risk, target trough concentrations are 16-24 ng/mL for 1st yr following transplantation
         b. After 1st yr following transplantation, target trough concentrations 12-20 ng/mL
2. Everolimus\textsuperscript{27,29,30}
   i. Zortress\textsuperscript{®} FDA approval (2010): prophylaxis of organ rejection in adult patients at low-
      moderate immunologic risk receiving a kidney transplant\textsuperscript{27}
      a. For combination with basiliximab and concurrently with reduced doses of CsA & CCS
   ii. Afinitor\textsuperscript{®} FDA approval (2009): indicated for use in various malignancies\textsuperscript{30}
      a. Advanced HER2- negative breast cancer
      b. Progressive neuroendocrine tumors of pancreatic origin
      c. Advanced renal cell carcinoma
      d. Renal angiomyolipoma and tuberous sclerosis complex
      e. Tuberous sclerosis complex with subependymal giant cell astrocytoma
   iii. Dosing in renal transplantation: 0.75 mg twice daily
   iv. Therapeutic drug monitoring: target trough concentrations 3-8 ng/mL
3. Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus</th>
<th>Everolimus</th>
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<tbody>
<tr>
<td>Half-life</td>
<td>~60 hours</td>
<td>~ 30 hours</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP 3A4; P-glycoprotein; 7 major metabolites*</td>
<td>CYP 3A4; P-glycoprotein; 2 main metabolites*</td>
</tr>
<tr>
<td>Excretion</td>
<td>&gt; 90% feces</td>
<td>80% feces</td>
</tr>
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* Metabolites contribute little to immunosuppressive activity

4. Side effect profile\textsuperscript{15,26,27,28,29}
   i. Dyslipidemia (43-57%)
   ii. Proteinuria (48%)
   iii. Mouth ulcers/aphthous stomatitis (8-46%)
   iv. Bone marrow suppression (14-30%)
   v. Delayed wound healing (3-20%)
   vi. New-onset diabetes mellitus (< 10%)
   vii. Surgical complications (9-15%)

C. Place in therapy for kidney transplantation
1. Kidney disease improving global outcomes (KDIGO\textsuperscript{®}) guidelines recommendations\textsuperscript{15}
   i. Not recommended as maintenance therapy
      a. Not shown to improve patient outcomes when used either as replacement for antimetabolites or CNIs, or as add-on therapy
      b. Combined use with CNIs potentiate nephrotoxicity
      c. Adverse effects limit use
2. Practical clinical use\textsuperscript{31,32}
   i. Option for use in patients suffering from CNI-related side effects
   ii. mTORI combination therapy with early CNI withdrawal (WD) most promising option for use to provide efficacy and safety
   iii. With de novo use, loading doses avoided, if possible, to prevent wound healing complications and delayed graft function
   iv. Goal SRL trough concentrations typically maintained between 4-10 ng/mL depending on concomitant immunosuppressant therapy
THE RESOLVE: EVIDENCE FOR USE OF MTOR INHIBITORS FOR SKIN CANCER RISK REDUCTION

VII. Mathew et al. – 200433 (Appendix A)
   A. Meta-analysis of five multicenter studies (3 Phase 3 and 2 Phase 2 trials) in KTRs
   B. Comparison of:
      1. SRL- vs. CsA-based therapy
      2. CsA + SRL 2 mg/day vs. SRL 5 mg/day vs. placebo vs. AZA
      3. SRL + CsA vs. SRL + CsA WD
   C. Duration: 2 yr
   D. Results:
      1. Lower incidence of total and skin malignancies in patients receiving SRL regimens
      2. Lower incidence of total, skin, and other malignancies in SRL + CsA WD compared with SRL + CsA

VIII. Kauffman et al. – 200534 (Appendix A)
   A. Retrospective analysis of primary KTRs reported to the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) database
   B. Comparison of:
      1. mTORI ± antimetabolite (n = 504)
      2. mTORI + CNI ± antimetabolite (n = 2,321)
      3. CNI ± antimetabolite (n = 30,424)
   C. Duration: 963 days
   D. Results:
      1. Statistically significant lower incidence of all de novo malignancies and non-skin solid malignancies in patients receiving mTORI containing regimens
      2. Lower rates of skin malignancies in patients receiving mTORI containing regimens

IX. Campistol et al. – 200635,36 (Appendix A)
   A. Prospective, multi-center, international, randomized, open-label trial in adolescents and adults who underwent kidney transplantation within 3 mos and received CsA-SRL-CCS
   B. Treatment arms:
      1. CsA-SRL-CCS continuation (n = 215)
      2. CsA WD (n = 215)
   C. Duration: 5 yr
   D. Results:
      1. Incidence of any skin malignancies statistically significantly less in CsA WD arm in both the intent-to-treat (ITT) and on-therapy (OT) populations
      2. Time to 1st skin malignancy statistically significantly lower in CsA WD arm in ITT and OT populations
      3. Higher percent with any skin and non-skin malignancy-free survival in CsA WD arm in ITT and OT populations
| **Objective** | Examine malignancy rates in KTRs at 2 yr after conversion to SRL-based, CNI-free regimen compared with CNI-based regimen |
| **Design** | Prospective, multicenter, intercontinental, randomized, open-label, comparative study |
| **Population** | **Inclusion:** ≥ 13 yr, kidney transplantation ≤ 6-120 mos, CNI + CCS + AZA (≥ 50 mg/day) or mycophenolate mofetil (MMF, ≥ 500 mg/day) for ≥ 12 wk, GFR ≥ 20 mL/min, baseline biopsy ≤ 16 wk of randomization  
**Exclusion:** treatment for biopsy-confirmed/clinically diagnosed acute rejection (AR) ≤ 12 wk of enrollment, history of post-transplant lymphoproliferative disease (PTLD) or known/suspected malignancy ≤ 5 yr before screening |
| **Methods** |  
**Enrollment:** 2/2002-3/2004  
**Randomization and treatment arms:**  
- Convert to SRL-based IS or continue CNI-based therapy for 104 (extended to 208) wk  
- Stratified by baseline-calculated GFR of 20-40 mL/min or > 40 mL/min  
- SRL conversion  
  - Day 1: 12-20 mg; day 2: 4-8 mg/day until SRL target trough level achieved  
  - Target trough concentration: 8-20 ng/mL  
  - After target SRL trough achieved, max MMF, 1.5 g/day, or AZA, 75 mg/day; thereafter, could be discontinued  
- CNI continuation: CsA target trough 50-250 ng/mL, TAC target trough 4-10 ng/mL; CNI switching permitted  
- Both groups received CCS doses of 2.5-15 mg/day  
| **Outcomes** |  
- Malignancy rates at 2 yrs  
- Post Hoc Analyses  
  - Malignancy rates based on time of study drug exposure (# malignancies/100 person-yr of exposure)  
  - Malignancy rates in KTRs without prior history of the same malignancy that developed during study  
  - Impact of age, time from transplant to treatment, presence of malignancy, & combination of treatment & presence of malignancy assessed  
| **Statistics** |  
- p < 0.05 considered significant (one-tailed test)  
- ANOVA used for assessment of confounding effects  
| **Results** |  
- **ITT:** n = 830; SRL, n = 555; CNI, n = 275  
- **Received study medication:** n = 824; SRL, n = 551; CNI, n = 273  
- **Subgroup excluding patients with prior history of same malignancy occurring during study:** n = 804; SRL, n = 542; CNI, n = 262  
**Baseline characteristics:**  
- Similar between treatment groups within each GFR stratum with following exceptions:  
  - GFR 20-40 mL/min stratum:  
    - Greater Grade I & II baseline chronic allograft nephropathy (CAN) score in CNI group (48.2% vs. 20.4%; 33.3% vs. 25.9%)  
    - Greater Grade III baseline CAN score in SRL group (50% vs. 11.1%)  
  - GFR > 40 mL/min stratum:  
    - Greater Grade III baseline CAN in SRL group (12.4% vs. 9.2%)  
- Mean time from transplant to randomization: SRL, 38.8 mos (3.2 yr); CNI, 36.3 mos (3.0 yr)  
- GFR 20-40 mL/min stratum: enrollment halted due to primary safety endpoint of acute rejection (AR), graft loss, or death reached by 8/48 (16.7%) in SRL group vs. 0/25 (0%) in CNI group (p = 0.045)  
**Malignancy at 2 yr:**  
- Total, 51/824 (6.2%); SRL, 21/551 (3.8%); CNI, 30/273 (11%)  
- NMSC: SRL, 12/551 (2.2%); CNI, 22/273 (8.1%)  
- Melanoma: SRL, 0/551 (0%); CNI, 3/273 (1.1%); p = 0.036  
**Post hoc analyses:**  
- # malignancies/100 person-yr of exposure, all patients (Figure A)  
- # malignancies/100 person-yr of exposure, subgroup without history of same malignancy (Figure B)  

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Malignancy rates at 24 mos/100 person-yr of exposure: (A) all patients, (B) patients without history of previous malignancy.

AOM: all other malignancies, includes solid organ, hematologic, and melanoma

- Malignancy rates based on mean total exposure; mean total exposure: SRL - 1.8 yr; CNI - 2 yr
  - Total exposure > 2.2 yr: SRL vs. CNI (4.3% vs. 14.6%, p < 0.001)
  - Total exposure ≥ 2 yr & < 2.2 yr: SRL vs. CNI (1% vs 3.4%, p < 0.001)
  - Total exposure < 2 yr: SRL vs. CNI (4.7% vs. 11%, p < 0.001)
- Age and time from transplant were predictors of malignancy development
  - Age: patients who developed malignancy vs. those who did not (56.7 vs. 42 yr, p < 0.001)
    - Mean age of patients who developed malignancy: SRL, 55.4 yr vs. CNI, 58.0 yr; p = 0.488
  - Time from transplant: patients who developed malignancy vs. those who did not (3.7 vs. 3.1 yr, p = 0.035)
    - Mean time from transplant of patient who developed malignancy: SRL, 4.6 yr vs. CNI, 2.9 yr; p = 0.005
- AEs: SRL, 98.2%; CNI, 94.9%; p = 0.014
  - Discontinuations due to AEs: SRL, 110/551 (20%); CNI, 29/273 (10.6%)
  - Higher infection rate in SRL arm: 77.5% vs. 67%, p = 0.002
    - Between mos 0-6: SRL, 59.3% ; CNI, 39.6%; p < 0.001
    - Between mos 6-24: SRL, 58.8%; CNI, 56.4%; p = 0.549

Author's Conclusion: Conversion to SRL lowers the rate of malignancy in KTRs and may provide short-term reduction in the risk of developing malignancy

Reviewer's Conclusion: Conversion to SRL lowers the rate of NMSC and other malignancies in KTRs but may result in other serious complications including graft dysfunction and infection.

Critique:
- Longer term follow-up would have been more appropriate
- Baseline characteristics relating to risk for development of skin cancer not provided
- No data on SRL or CNI levels or differences in levels depending on time post-transplant
- No data number of patients receiving AZA vs. MMF in combination with CNI prior to study enrollment
- Differences in discontinuation rates
**Objective**
Assess efficacy of SRL for secondary prevention of skin cancers in KTRs receiving CNIs

**Design**
Phase 3, multicenter, randomized, open-label conducted in Europe

**Population**
Inclusion: KTRs with stable kidney function receiving CNIs & had ≥ 1 invasive post-transplant cutaneous SCC

Exclusion: in situ lesions, such as Bowen’s disease & premalignant keratosis, or metastatic SCC, multorgan transplantation, history of rejection ≤ 6 mos, poor graft function (estimated GFR < 30 mL/min, or 24 hr protein excretion of > 1 g), uncontrolled hyperlipidemia, hematologic or hepatic disorders, retinoid treatment

**Methods**
Randomization and treatment arms
- Convert to SRL-based IS or continue CNI-based therapy
- SRL conversion
  - Conversion according to routine practice at each center
  - Target SRL trough level: 6-12 ng/mL
  - Conversion method: rapid = CNI discontinuation ≤ 7 days; progressive = CNI discontinuation > 7 days
- CNI continuation: CsA target trough 75-125 ng/mL, TAC target trough 4-7 ng/mL

Study Evaluations
- Dermatology & nephrology examinations at enrollment & every 3 mos
- Dermatologic exam recordings: Fitzpatrick skin type, eye & hair color, sun exposure, tanning-bed use, tropical area residence > 6 mos, # of histologically determined skin tumors before & after transplantation
- Nephrology exam recordings: immunosuppressive medication doses, history of AR; during initial evaluation, serum creatinine (SrCr), 24-hr protein excretion, SRL or CNI levels
- If undergone > 1 transplant, duration of IS
- CNI group: trough levels every 3 mos
- SRL group: weekly trough levels for 1st 2 wk, monthly for 1st 3 mos, then every 3 mos

**Outcomes**
Primary efficacy endpoint: survival free of new cutaneous SCC at 2 yr
Secondary endpoints:
- Time to onset of new cutaneous SCC
- Occurrence of other skin and nonskin tumors
- Graft function

Safety endpoints: adverse events

**Statistics**
Data pooled from two studies: patients with 1 cutaneous SCC lesion and patients with multiple SCC lesions
- Mann-Whitney test for quantitative variables
- Fisher’s exact test for qualitative variables
- Main evaluation criteria analyzed in intention-to-treat population
- Nonparametric maximum-likelihood estimation to analyze rate of survival free of new cutaneous SCC on interval censored data
- Log-tauquet test to compare to study groups
- For benefit-risk balance, counted # of cutaneous SCC and treatment-related serious adverse events during therapy period & for 3 mos after discontinuation
- Two-sided P value of < 0.05 considered statistically significant

**Results**
- ITT: n = 120; SRL conversion, n = 64; CNI continuation, n = 56
- At 2 yr: n = 86; SRL conversion, n = 42; CNI continuation, n = 44
- Rapid SRL conversion, n = 37; progressive SRL conversion, n = 27
- CsA, n = 84 (mean trough 90.6 ng/mL); TAC, n = 36 (mean trough 6.9 ng/mL)

Baseline characteristics
- Similar between treatment groups with the following exceptions:
  - Greater % with Fitzpatrick skin type IV in SRL group (17 [27%] vs. 10 [18%])
  - 290 diagnosed SCCs; 55% had a single lesion, 45% had multiple lesions
  - Median length of IS prior to randomization: SRL, 148.6 mos (12.4 yr); CNI, 142.9 mos (11.9 yr)

Primary Efficacy Endpoint
- Survival free of new SCC longer in SRL group, hazard ratio (HR) 0.37 [95% confidence interval (CI) 0.16-0.85], study adjusted HR of 0.38 [95% CI 0.17-0.84]
  - Single SCC group: survival free of new SCC longer in SRL group, HR 0.03, 95% CI 0.0-0.91
  - Multiple SCCs group: survival free of new SCC not different between treatment groups, HR 0.67 (95% CI 0.29-1.54)
  - Effect of SRL not significantly different between stratification groups (P = 0.54 for interaction between study and treatment group)
- New SCC: SRL, 14/64 (22%); CNI, 22/56 (39%); relative risk (RR) 0.56 [95% CI 0.32-0.98]
  - New cutaneous SCC developed in 6 in the SRL group after SRL WD
  - 1 metastatic SCC developed in SRL group after SRL WD
  - At 2 yr, new SCC: SRL, 20/42 (47.6%); CNI, 31/44 (70.5%); p = 0.048
  - 13 SCCs in SRL group; 39 in CNI group
  - 8 in CNI group switched to SRL group after development of malignancy

Secondary Endpoints
- Time to onset of new cutaneous SCC: longer in SRL group (15 vs. 7 mos, p = 0.02)
- Occurrence of other skin and non-skin tumors
  - At 2 yr, number of other skin tumors: SRL, 24; CNI, 45
  - At 2 yr, number of non-skin tumors: SRL, 3; CNI, 3
- Graft function: no episodes of AR

Safety Endpoints
- Adverse events (AEs)
  - SRL group: almost all had ≥ 1 AE
    - 23% (n = 15) resulted in discontinuation within median of 2.5 mos
    - Rapid vs. progressive conversion discontinuation rate: 11/37 (30%) vs. 4/27 (15%), p = 0.24
    - Rapid vs. progressive conversion serious AEs: 24/37 (65%) vs. 8/27 (30%), p = 0.01
  - Serious AEs: SRL, 60; CNI, 14
    - Subjects with pneumonitis: SRL, 13/64 (20%); CNI, 1/56 (1.7%)

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<tr>
<th>Author’s Conclusion</th>
<th>Conversion from CNIs to SRL decreased risk of new SCC and delayed occurrence of lesions; however, adverse effects of SRL led to large percentage of drug discontinuation. Earlier conversion to SRL after initial SCC diagnosis may provide greater efficacy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reviewer’s Conclusion</td>
<td>SRL decreases risk of new SCC early after conversion and provides benefit in early and later stages of SCC even after large cumulative doses of IS therapy. Best benefit of conversion to SRL may be soon after initial diagnosis of SCC but may result in occurrence of intolerable side effects. Progressive conversion appears to reduce the risk of developing serious AEs.</td>
</tr>
</tbody>
</table>
| Critique            | Differences in baseline characteristics between groups  
Not blinded  
No specific protocol for conversion to SRL  
Longer follow-up would have been more appropriate  
Differences in discontinuation rate between groups |

<table>
<thead>
<tr>
<th>Objective</th>
<th>Compare rates of new NMSC lesions with SRL conversion vs. CNI continuation in stable KTRs with high skin cancer risk</th>
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<tr>
<td>Design</td>
<td>Prospective, multicenter, randomized, controlled, open-label conducted in Australia, New Zealand, and the U.S.</td>
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</table>
| Population | **Inclusion**: ≥ 18 yr, kidney transplant ≥ 21 yr, NMSC ≤ 3 yr of enrollment, CNI-based therapy ≥ 1 yr, consistent IS regimen ≥ 1 mos, Nankivell GFR ≥ 40 mL/min, proteinuria ≤ 500 mg/day  
**Exclusion**: malignancy other than NMSC ≤ 3 yr of enrollment, history of NMSC with metastatic disease or excessive # of lesions (> 20 in previous yr), systemic retinoid therapy, field treatment with topic agents, photodynamic therapy, medium-depth chemical peels or laser resurfacing ≤ 12 mos before enrollment |
Randomization and treatment arms  
- Convert to SRL from CNI-based regimen or CNI continuation  
- SRL conversion:  
  - Day 1: discontinued CNI & given SRL loading dose of 6-12 mg, then 2-4 mg daily thereafter  
  - Target SRL trough 5-15 ng/mL  
  - MMF decreased to ≤ 1.5g/day, MPS to ≤ 1080 mg/day, or AZA to ≤ 75mg/day once SRL trough 5 ng/mL  
- CNI continuation: baseline therapy maintained; investigator’s discretion to adjust or switch doses  
- Both groups  
  - Antimetabolites switched, adjusted, or discontinued as necessary  
  - CCS: if receiving at randomization, minimum dose 2.5 mg/day & withdrawal prohibited; if not receiving at randomization, initiation permissible  
- Stratification by # of new NMSC lesion in previous 12 mos: 0-5 or 6-20  
Duration: 2 yr treatment phase + 1 mos follow-up; treatment phase amended to at least 1yr  
Study evaluations  
- Physical exams and labs at baseline and regular intervals  
- Dermatology examinations every 3 mos  
- All suspected NMSC lesions reported at time of biopsy or excision/treatment  
- Patients who discontinued protocol-assigned treatment early, but continued study participation evaluated at:  
  - (1) time of treatment discontinuation; (2) 4 wk after discontinuation; (3) 24, 52, 76, and 104 wk following randomization |
| Outcomes  | Primary efficacy endpoint: # of new biopsy-confirmed NMSC lesions/patient/yr  
Secondary endpoints:  
- Time to 1st new biopsy-confirmed NMSC lesion  
- # of lesions recurring at site of previously treated lesion  
Additional endpoints: change from baseline in calculated creatinine clearance (CrCl) and SrCr, change in urine protein:creatinine ratio, graft loss, death, biopsy confirmed AR  
Safety endpoints: incidence of infection, wound healing complications, other malignancies |
| Statistics | - Designed with 90% power to detect mean difference of 1 new lesion  
- Two-sided P value of < 0.05 considered statistically significant  
- Assuming SD of 2 lesions/year, sample size of 90 patients/group needed  
- Primary end point between-group difference compared using Poisson regression model adjusted by baseline NMSC stratum  
- Time to 1st new biopsy-confirmed NMSC lesion displayed with Kaplan-Meier curves and compared using Cox proportional hazards method adjusted for baseline NMSC stratum  
- ANCOVA to compare GFR and serum creatinine change from baseline, with baseline as covariate  
- Wilcoxon rank sum test used for between-group comparison for protein:creatinine ratio |
| Results   | - ITT: n = 86; SRL conversion, n = 39; CNI continuation, n = 47  
- On-therapy at 2 yr (OT): n = 32; SRL conversion, n = 8; CNI continuation, n = 24  
- Mean length of follow-up for ITT: SRL, 1.68 yr; CNI, 1.74 yr (p = 0.127)  
- Mean length of follow-up for OT: SRL, 0.95 yr; CNI, 1.62 yr (p < 0.001)  
Baseline characteristics  
- Similar between treatment groups with the following exceptions:  
  - Retransplantation higher in CNI group: 8/47 (17%) vs. 4/39 (10%)  
  - AZA use higher in CNI group: 15/47 (31.9%) vs. 8/39 (20.5%)  
  - Mean time after transplant: 112 mos (9.3 yr)  
  - Mean SRL trough concentrations: 7.1-12.6 ng/mL over course of study |
• Mean CsA trough concentrations: 83.8-96.9 ng/mL over course of study
• Mean TAC trough concentrations: 5.8-8 ng/mL over course of study

Primary Endpoint
• Lower rate of new biopsy confirmed NMSC lesions/patient-yr in SRL arm (ITT: 1.31 vs. 2.48, p = 0.022; OT: 1.35 vs. 2.5, p = 0.072)
  • Rate of new biopsy confirmed SCC lesions/patient-yr: ITT-SRL, 0.88; CNI, 1.71; p = 0.038; OT-SRL, 0.95; CNI, 1.68; p = 0.145
  • Rate of new biopsy confirmed BCC lesions/patient-yr: ITT-SRL, 0.43; CNI, 0.77; p = 0.104; OT-SRL, 0.41; CNI, 0.82; p = 0.095
• Proportion lesion-free during study: SRL, 43.6%; CNI, 19.1%, p = 0.015

Secondary Endpoints
• Time to 1st new biopsy-confirmed NMSC lesion
  • Median time to 1st new lesion (ITT): SRL, 380 days; CNI, 163 days, p = 0.047
  • Median time to 1st new SCC (ITT): SRL, 750 days; CNI, 189 days, p = 0.012
• # of lesions recurring at site of previously treated lesion
• No treatment difference (ITT): SRL, 0.107 lesions/patient-yr; CNI, 0.134 lesions/patient-yr, p=0.748

Additional Endpoints
• Mean change in calculated creatinine clearance from baseline
  • ITT: no significant difference between groups at 6,12, or 24 mos
  • OT: significant between-group difference at month 12:SRL, +3.88; CNI, -1.82, p = 0.029
• Median urine protein:creatinine ratio: SRL, 0.11-0.14; CNI, 0.08-0.12
  • Wk 104: SRL, 0.14; CNI, 0.12, p = 0.03
• Graft loss: SRL, n = 2; CNI, n = 1; p = 0.59
• Death: 1 in both groups
• AR: 1 episode in CNI group
• AEs resulting in discontinuation: SRL, 18/39 (42.6%); CNI, 0/47 (0%), p < 0.001

Safety Endpoints
• Delayed wound healing (ITT): SRL, 4/39 (10%); CNI, 3/47 (6%), p = 0.697

Author's Conclusion
Results from this study in combination with other studies suggest benefit in relation to reduction of skin malignancies with use of sirolimus-based immunsuppressive regimens.

Reviewer's Conclusion
SRL decreases the incidence of new NMSC and SCC risk and significantly prolongs the time to development of new lesion, but also, significantly increases the incidence of side effects.

Critique
• Dermatologists not blinded
• Differences in baseline characteristics between groups
• Longer term follow-up may have been more appropriate
• Data not presented for different stratification groups
• Differences in discontinuation rate between groups
• Data on time to treatment discontinuation not provided
X. Guideline recommendations for changes in immunosuppressive regimen for OTRs with skin cancer

A. 2012 NCCN® clinical practice guidelines in oncology: basal cell and squamous cell skin cancers
   1. Consider reduction of doses of immunosuppressive agents in solid OTRs
   2. Consider minimizing doses of CNIs &/or antimetabolites in favor of mTORIs in solid OTRs

B. 2009 KDIGO® clinical practice guidelines for the care of KTRs
   1. Consider reducing immunosuppressive medications in KTRs with cancer

C. 2009 Swiss clinical practice guidelines for skin cancer in OTRs
   1. Consider reduction of IS in all cases of recurrent or aggressive skin cancer, particularly SCC
   2. Consider switch from CNIs to mTORIs in OTRs with stable transplant function with moderate-severe cutaneous carcinogenesis of SCC
   3. Consider switch from AZA to MMF in OTRs with stable transplant function with moderate-severe cutaneous carcinogenesis of SCC

D. 2004 International Transplant –Skin Cancer Collaborative (ITSCC) and European Skin Care in Organ Transplant Patients (SCOP) Network guidelines for the management of SCC in OTRs
   1. Consider decreasing IS in cases of life-threatening skin cancers, rapid development of multiple SCCs, SCC with satellite lesions, and SCC with palpable lymphadenopathy

XI. Final recommendations

A. Recommendations for mTORI use in KTRs with NMSC
   1. Decreasing doses of concomitant immunosuppressants, if suitable
   2. If on AZA, switch to MPA
   3. Initiation of mTORI using a progressive approach
   4. Avoidance of mTORI loading doses
   5. Targeting lowest trough concentrations of mTORIs possible
<table>
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<tr>
<th>Trial &amp; Year</th>
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<th>Population</th>
<th>Treatment Arms</th>
<th>Follow-up</th>
<th>Results (p-value)</th>
</tr>
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</table>
| Mathew et al. 2004  | Meta-analysis; 5 multi-center studies       | KTRs             | A) SRL- vs. CsA-based therapy                                                  | 2 yr      | • Incidence of malignancy, %  
  • All malignancies:  
    • A) SRL, 0 vs. 5  
    • B) SRL 2 mg/day, 5 vs. 5 mg/day, 6.4 vs. placebo, 8.5 vs. AZA, 5.5  
    • C) SRL + CsA, 9.8 vs. CsA WD, 4.2 (< 0.05)  
  • Skin malignancy, excluding melanoma:  
    • A) SRL, 0 vs. 1.3  
    • B) SRL 2 mg/day, 2\(^a\) vs. 5\(^b\) mg/day, 2.8 vs. placebo, 6.9 vs. AZA, 4.3  
    • C) SRL + CsA, 5.1 vs. CsA WD, 2.3  
  • Other malignancies, excluding PTLD\(^c\):  
    • A) SRL, 0 vs. 3.8  
    • B) SRL 2 mg/day, 1.8 vs. 5 mg/day, 1.6 vs. placebo, 0.8 vs. AZA, 0.6  
    • C) SRL + CsA, 3.3 vs. CsA WD, 1.4 |
| Kauffman et al. 2005| Retrospective analysis                      | Inclusion: primary KTRs reported to OPTN/UNOS\(^d\), minimum survival of 8 days | A) mTORI ± antimitabolite n = 504                                               | 963 days  | • Development of de novo malignancy  
  • All malignancies, %:  
    • mTORI, 0.6 vs. CNI, 1.81 (0.041)  
    • mTORI + CNI, 0.6 vs. CNI, 1.81 (<0.0001)  
  • Nonskin solid malignancies\(^i\), %:  
    • mTORI, 0 vs. CNI, 1 (0.011)  
    • mTORI + CNI, 0.47 vs. CNI, 1 (0.0125)  
  • Skin malignancies\(^e\), n [%]:  
    • mTORI, 3 [0.6] vs. CNI, 252 [0.8]  
    • mTORI + CNI, 3 [0.1] vs. CNI, 252 [0.8] |

\(^{a}\) p < 0.01 vs. placebo; \(^{b}\) p < 0.05 vs. placebo; \(^{c}\) PTLD: post-transplant lymphoproliferative disease; \(^{d}\) OPTN/UNOS: Organ Procurement and Transplantation Network/United Network for Organ Sharing; \(^{e}\) includes cutaneous Kaposi’s sarcoma and melanoma;
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<td>Campistol et al. (^{35,36})</td>
<td>Multi-center, prospective, International, randomized, open-label</td>
<td>Inclusion: ≥ 13 yr, kidney transplantation within 3 mos, received SRL-CsA-DDI after transplantation &lt;br&gt; Exclusion: major infection, chronic antiarrhythmic therapy for ventricular arrhythmia, history of malignancy, induction therapy, gastrointestinal disorder</td>
<td>A) CsA WD @ 3 mos (SRL-DDI) (ITT, n = 215)  &lt;br&gt; B) CsA-SRL-DDI (ITT, n = 215)</td>
<td>5 yr</td>
<td>• Incidence of any skin malignancy  &lt;br&gt; • # malignancies, mean annualized rate (#/1000 patients/yr)  &lt;br&gt; • OT: SRL-DDI, 22.1 vs. 151.6 (&lt;0.001)  &lt;br&gt; • ITT: SRL-DDI, 39 vs. 109 (&lt;0.001)  &lt;br&gt; • Time to 1st malignancy, days  &lt;br&gt; • OT: SRL-DDI, 1248.5 vs. 401.5 (0.021)  &lt;br&gt; • ITT: SRL-DDI, 1126 vs. 491 (0.007)  &lt;br&gt; • Malignancy-free survival, %  &lt;br&gt; • OT: SRL-DDI, 93.96 vs. 90.3 (0.055)  &lt;br&gt; • ITT: SRL-DDI, 91.68 vs. 90.57 (0.459)</td>
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<tr>
<td>Salgo et al. (^{41})</td>
<td>Single-center, prospective, randomized, assessor-blinded, controlled</td>
<td>Inclusion: Adult KTRs, transplantation ≤ 1 yr, no rejection within 6 mos, stable renal function, existence of premalignant skin dysplasia  &lt;br&gt; Exclusion: pregnancy, anemia, leucopenia, thrombocytopenia, previous SRL therapy</td>
<td>A) SRL conversion +CCS (ITT, n = 25; OT, n = 16)  &lt;br&gt; B) Continue current IS (ITT, n = 19; OT, n = 17)</td>
<td>12 mos</td>
<td>• Improvement in premalignant skin dysplasia, n (OT): SRL, 11 vs. 0 (&lt; 0.0001)  &lt;br&gt; • New NMSC, n (OT): SRL, 1 vs. 8 (0.0167)  &lt;br&gt; • Rejection, n (OT): SRL, 0 vs. 0 (NS)  &lt;br&gt; • Δ creatinine, mg/dL (OT): SRL, +0.02 (NS); current IS, -0.08 (NS)  &lt;br&gt; • *Cholesterol, mg/dL  &lt;br&gt; • Δ TC(^{\dagger}) (OT): SRL, +30 (0.004); current IS, +14 (NS)  &lt;br&gt; • Δ HDL(^{\ddagger}) (OT): SRL, -4.3 (NS); current IS, 0 (NS)  &lt;br&gt; • Δ LDL(^{\S}) (OT): SRL, +29 (0.004); current IS, +31 (0.02)  &lt;br&gt; • Δ TG(^{\I}) (OT): SRL, +70 (0.001); current IS, -16 (NS)  &lt;br&gt; • *Δ proteinuria, g/day: ITT – SRL, +0.5 (0.009); OT – SRL, +0.17 (NS); current IS, 0.19 (NS)</td>
</tr>
</tbody>
</table>

\(^*\) Data presented as median; \(^*\) Data presented as mean; \(^\dagger\) TC: total cholesterol; \(^\ddagger\) HDL: high density lipoprotein cholesterol; \(^\S\) LDL: low density lipoprotein cholesterol; \(^\I\) TG: triglycerides
REFERENCES


