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The use of Sirolimus as Secondary Prevention of Nonmelanoma Skin Cancer in Renal Transplant Recipients

Tiffany Chan

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Abstract

Background: Nonmelanoma skin cancer is the most prevalent post-transplant malignancy found in renal transplant recipients. Long term immunosuppressant therapy, previous history of nonmelanoma skin cancer and UV exposure are the greatest drivers of these malignancies in renal transplant recipients compared to the general population. Squamous cell carcinoma is the most prevalent type of nonmelanoma skin cancer lesions that can lead to increased morbidity and metastasis in this population. Sirolimus is a relatively new immunosuppressant that is known to have anti-tumor effects, especially in the instance of skin cancer. Will sirolimus reduce the recurrence of nonmelanoma skin cancer in renal transplant recipients with a previous history of nonmelanoma skin cancer?

Method: An extensive medical literature search was completed using MEDLINE, CINAHL, EBSCO, and Web of Knowledge. Search terms used included skin cancer, skin neoplasm, organ transplant, renal transplant, and sirolimus. Relevant articles were further evaluated for quality using the GRADE criteria.

Results: Three randomized controlled trials met the inclusion criteria of the systematic review. The studies showed a decreased incidence of nonmelanoma skin cancer in renal transplant recipients with a history of nonmelanoma skin cancer. One study demonstrated a significantly longer survival free of squamous cell carcinoma in the sirolimus group compared to calcineurin inhibitor therapy. Another study found a significantly decreased rate of nonmelanoma skin cancer in the sirolimus group. All studies observed an increased incidence of adverse drug reactions in the sirolimus group that led to high discontinuation rates. The overall quality of evidence was low after assessing each study with GRADE criteria.

Conclusion: The findings suggest that sirolimus is effective at reducing the recurrence of nonmelanoma skin cancer lesions in renal transplant recipients with a history of nonmelanoma skin cancer. While there appears to be some significance for sirolimus conversion of renal transplant recipients with nonmelanoma skin cancer, better quality research is necessary to determine the long term effects of sirolimus in renal transplant patients. Further studies are needed to determine when sirolimus should be initiated in patients to prevent skin cancer and treatment duration.
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The use of Sirolimus as Secondary Prevention of Nonmelanoma Skin Cancer in Renal Transplant Recipients

Tiffany Chan

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 2013 Faculty Advisor: Dr. Mark Pedemonte Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

1
Biography

[Redacted for privacy]
Abstract

Background: Nonmelanoma skin cancer is the most prevalent post-transplant malignancy found in renal transplant recipients. Long term immunosuppressant therapy, previous history of nonmelanoma skin cancer and UV exposure are the greatest drivers of these malignancies in renal transplant recipients compared to the general population. Squamous cell carcinoma is the most prevalent type of nonmelanoma skin cancer lesions that can lead to increased morbidity and metastasis in this population. Sirolimus is a relatively new immunosuppressant that is known to have anti-tumor effects, especially in the instance of skin cancer. Will sirolimus reduce the recurrence of nonmelanoma skin cancer in renal transplant recipients with a previous history of nonmelanoma skin cancer?

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Results: Three randomized controlled trials met the inclusion criteria of the systematic review. The studies showed a decreased incidence of nonmelanoma skin cancer in renal transplant recipients with a history of nonmelanoma skin cancer. One study demonstrated a significantly longer survival free of squamous cell carcinoma in the sirolimus group compared to calcineurin inhibitor therapy. Another study found a significantly decreased rate of nonmelanoma skin cancer in the sirolimus group. All studies observed an increased incidence of adverse drug reactions in the sirolimus group that led to high discontinuation rates. The overall quality of evidence was low after assessing each study with GRADE criteria.

Conclusion: The findings suggest that sirolimus is effective at reducing the recurrence of nonmelanoma skin cancer lesions in renal transplant recipients with a history of nonmelanoma skin cancer. While there appears to be some significance for sirolimus conversion of renal transplant recipients with nonmelanoma skin cancer, better quality research is necessary to determine the long term effects of sirolimus in renal transplant patients. Further studies are needed to determine when sirolimus should be initiated in patients to prevent skin cancer and treatment duration.

Keywords: Sirolimus, renal transplant recipients, skin cancer, skin neoplasm
Acknowledgements

[Redacted for privacy]
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Table I: GRADE Evidence Profile

List of Abbreviations

ADR..............................................................................................................Adverse drug reaction
CNI............................................................................................................Calcineurin Inhibitor
mTOR.......................................................................................................Mammalian Target of Rapamycin
NMSC.......................................................................................................Nonmelanoma Skin Cancer
RCT..........................................................................................................Randomized Control Trial
SCC..........................................................................................................Squamous Cell Carcinoma
The use of Sirolimus as Secondary Prevention in Nonmelanoma Skin Cancer in Renal Transplant Recipients

BACKGROUND

In 2010, there were 16,843 kidney transplants in the United States for patients age 20 years and older. Advances in immunosuppressant therapy have improved organ transplant outcomes. Graft failure rates are at an all-time low and long term survival of kidney transplant recipients is increasing. Consequently, physicians have witnessed more long term complications, such as post-transplant malignancies. The most common type of post-transplant malignancy seen in renal transplant recipients is nonmelanoma skin cancer (NMSC). Nonmelanoma skin cancer, with squamous cell carcinoma (SCC) being the most prevalent, accounts for 95% of skin cancer found in organ transplant patients. One German study found a 20-fold increase in the incidence of nonmelanoma skin cancers among renal transplant recipients. Investigators have found that these skin cancers are more worrisome due to their increased incidence of recurrence and metastasis in renal transplant recipients.

The greatest drivers in the incidence of SCC lesions among this population are immunosuppressant therapy and UV exposure. Age, UV exposure, previous history of NMSC, history of sunburn, and skin type have been identified as predictive factors for NMSC in renal transplant recipients. Primary immunosuppressive prophylaxis includes calcineurin inhibitors (CNIs), mycophenolates, azathioprine, corticosteroids, mammalian target rapamycin inhibitors, and IL-2 receptor antibodies. Calcineurin inhibitors, such as cyclosporine and tacrolimus, have had an impact on the improved outcomes of organ transplant recipients. CNIs inhibit cytokine
production by binding to intracellular mediators and blocking T cell signals. Also, CNIs inhibit mitochondrial permeability transition pore (MPTP) channels, which are responsible for cell death. In cyclosporine treated mice, cyclosporine demonstrated an enhanced effect of tumor growth. Azathioprine and UVA light react together to form mutagenic metabolites that enhance photosensitivity of the skin. This enables UVA light to directly damage DNA, which in combination with photosensitivity, increases the incidence of SCC.

In 2008, the FDA approved a new immunosuppressant, sirolimus, for prophylaxis for renal transplant recipients. Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor. Mammalian target of rapamycin is a protein that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. Sirolimus acts to inhibit IL-2 mediated signal transduction to stop the proliferation of T cells and B cells. In contrast to cyclosporine, sirolimus inhibits the growth of malignant cells and has demonstrated reduced tumor growth. Studies have found that renal transplant recipients who converted to sirolimus therapy had a significantly reduced incidence of malignancy compared to other immunosuppressants. Among renal transplant recipients with a history of NMSC, is sirolimus effective in reducing the recurrence of nonmelanoma skin cancer?

METHODS

An extensive medical literature search was completed using MEDLINE, CINAHL, Evidence Based Medicine Review Multifile, and Web of Knowledge. Search terms used included skin cancer, skin neoplasm, organ transplant, renal transplant, and sirolimus. Inclusion criteria consisted of randomized control trials with renal transplant
recipients with a previous history of NMSC lesions, use of sirolimus as immunosuppressant therapy, and articles written in English. Studies that consisted of combination therapy with sirolimus and another immunosuppressant, other solid organ transplant recipients, and patients without a previous history of NMSC were excluded from the study. Relevant articles were further evaluated for quality using the GRADE criteria.13

RESULTS

The literature search yielded 25 studies for review. After screening for relevant articles, 15 non-relevant articles were excluded. Three studies14-16 met the inclusion criteria and were incorporated into the systematic review. All studies were randomized control trials (RCTs).

Euvrard et al study

This multicenter, randomized, open label trial14 investigated the efficacy of sirolimus in secondary prevention of skin cancer in renal transplant recipients. The study enrolled and randomized 129 patients and 120 patients were included in the primary analysis. Eligibility criteria included renal transplant recipients with stable graft function, a post-transplant history of SCC, and who are currently receiving CNI treatment. There were 64 patients assigned to the sirolimus group and 56 patients in the calcineurin inhibitor group. Patients were randomly assigned to continue receiving CNI therapy or to transition from CNI to sirolimus therapy. In the sirolimus group, CNI therapy was discontinued and sirolimus was added until blood concentrations of sirolimus reached 6 to 12ng per milliliter. Sirolimus conversion therapy was considered rapid if CNI was discontinued within 7 days and progressive if CNI was discontinued beyond 7 days.
Exclusion criteria included multiorgan transplants, patients with in situ lesions, graft rejection in the past 6 months, poor graft function, uncontrolled hyperlipidemia, hematologic or hepatic disorders, and retinoid treatment.\textsuperscript{14}

The primary outcome was survival, free of SCC at 2 years. Secondary outcomes included time until the development of new SCC, development of other skin cancer, graft function, and adverse drug events (ADRs) to sirolimus. Patients were examined by a nephrologist and dermatologist initially, and then every 3 months for 2 years. The dermatology examination included Fitzpatrick’s classification of skin type, sun exposure, and number of lesions before and after randomization. The nephrologist monitored the immunosuppressant dosage of each patient at their visit. The sirolimus group was monitored weekly for the first 2 weeks, monthly for the first 2 months, and every 3 months for the next 2 years.\textsuperscript{14}

Baseline characteristics were balanced between the two study groups. At baseline, 120 patients were diagnosed with SCC, of which 55\% had a single lesion, and 45\% had multiple lesions. Calcineurin inhibitor therapy included 84 patients on cyclosporine and 36 patients receiving tacrolimus.\textsuperscript{14}

The study determined the survival free of SCC, was significantly longer with sirolimus therapy compared to the CNI group (hazard ratio 0.37, 95\% CI 0.16 to 0.85). This was significant for patients with a single SCC (hazard ratio 0.03, 95\% CI 0.0 to 0.91), but not for those with multiple SCC (hazard ratio 0.67, 95\% CI 0.29 to 1.54). Development of new SCC occurred in 14 patients in the sirolimus group and 22 patients in the CNI group (RR= 0.56, 95\% CI 0.32 to 0.98). In the sirolimus group, 6 patients developed new SCC after sirolimus withdrawal.\textsuperscript{14}
The study found that more sirolimus patients experienced an ADR (60 serious adverse events vs 14 adverse events in the CNI group). Adverse drug events occurred in 37 out of 64 patients in the sirolimus group. This was more likely to occur with those patients who underwent rapid conversion compared to progressive conversion from CNI to sirolimus. Also, those who underwent rapid conversion had a higher discontinuation rate. The study decreased the sirolimus dose, which controlled most of the ADRs, but 15 patients (23%) discontinued after a median of 2.5 months. Some of the ADRs observed included edema, acne like lesions, aphthous ulcers, and proteinuria.  

The study concluded that switching to sirolimus from CNI decreased the risk and rate of SCC lesions. Because the study was inadequately powered, there were no significant differences between the groups concerning the rate of SCC. The authors suggest that early conversion to sirolimus is more efficacious for patients with newly diagnosed SCC.  

**Campbell et al study**  
This prospective, multicenter, open label, randomized control trial compared the rate and occurrence of NMSC in stable renal transplant patients who converted to sirolimus treatment to those currently on CNI therapy. The study was conducted in Australia, New Zealand, and the United States and was sponsored by Pfizer Pharmaceuticals. The primary outcome was the number of biopsies confirmed; NMSC lesions that occurred within the study duration of 1 year plus 1 month for follow up. The secondary outcomes included the rate for the first new NMSC lesion to occur.  

Patients who were renal transplant recipients within at least 1 year, 18 years or older, who are currently on CNI, and have a history of NMSC within the past 3 years,
were included in the study. The authors excluded those with unstable graft function, and other malignancies besides NMSC. Those receiving treatment for their skin lesions, such as retinoid treatment, phototherapy, topical agents, chemical peels, and laser treatments, were excluded from the study.¹⁵

Patients were stratified by the number of NMSC lesions within the last 1 year and then randomly assigned to sirolimus conversion or continuing calcineurin inhibitors. They were assigned to study groups using a computer generated program, Clinical Operation Randomization Environment. Those converting to sirolimus discontinued their CNI and were dosed accordingly until whole blood trough concentrations of 5ng/mL were maintained.¹⁵

Baseline characteristics were similar between the study groups. From Sept 2005 to Oct 2007, eighty seven patients were enrolled and randomized. One patient was randomized in error. With 86 patients included in the trial, 39 patients were assigned to convert to sirolimus and 47 patients continued CNI therapy. Initially, follow up was to consist of a 2 year study duration plus 1 month follow up, but due to low enrollment and high discontinuation rate, follow up was reduced to 1 year study duration plus 1 month follow up. The most common reason for discontinuation in the sirolimus group was adverse drug reactions.¹⁵

The study found that the sirolimus group had a significantly lower yearly rate of new biopsy confirmed NMSC lesions compared to the CNI group (1.31 vs 2.48, p=0.022).¹⁴ Fewer patients developed new or recurrent NMSC lesions in the sirolimus group compared to the CNI group (56.4% vs 80.9%, RR= 0.07; p= 0.015) and new SCC (41.0% vs 70.2%, RR= 0.58; p= 0.006).¹⁵ The study¹⁵ found no significant difference
between groups concerning the incidence of any serious ADRs (sirolimus 38.5% vs CNI 44.7%, RR=0.86). Eighteen patients in the sirolimus group discontinued their assigned treatment due to adverse drug reactions. The most frequent ADRs observed were pneumonitis, diarrhea, and decreased tolerance.  

The authors concluded that switching to sirolimus lowered the amount of NMSC lesions that occurred in renal transplant recipients. The study was limited due to the high discontinuation rate in the sirolimus group. Factors that may have contributed to this include abrupt conversion to sirolimus from CNI, higher loading doses and blood concentrations higher than what is used in current practice, and patient related factors.  

The authors noted that the overall rate reduction of NMSC lesions was driven by lower SCC rates compared to BCC rates, but the study did not calculate a difference between these two lesions. Also, the authors speculate that CNI withdrawal after converting to sirolimus may have contributed to the decrease in the yearly incidence of NMSC lesions. CNIs and other immunosuppressants are thought to enhance tumor growth, while sirolimus interferes with angiogenesis and cancer cell growth. 

Salgo et al study  

This is a single center, prospective, single blinded randomized control trial that assessed whether switching to sirolimus decreased the progression of malignancies and the number of new NMSC lesions that occurred compared to other immunosuppressants. There were 44 patients enrolled in the study and randomly assigned to treatment groups. Patients were included in the study if they had stable renal function, were between 18 and 75 years, have a history of NMSC, actinic keratosis, verruca vulgaris, and had renal transplantation for more than 1 year. Those who underwent previous sirolimus therapy,
were pregnant or planning for pregnancy, and had hematologic disorders were excluded from the study. Patients were seen a dermatologist, who was blinded to treatment groups throughout the study. Dermatology visits occurred at baseline, 6 months, and 12 months, and involved the same dermatologist.¹⁶

Both study groups had similar baseline characteristics. There were 25 patients converted to sirolimus and 19 patients continuing their original immunosuppressant therapy. The study duration was 12 months.¹⁶

The secondary outcome the occurrence of new NMSC lesions within the 1 year study duration. Focus was placed on the secondary outcome due to its relevance to the clinical question. Development of new NMSC lesions occurred in 1 patient in the sirolimus group and 8 patients in the control group. The most common ADRs that occurred were aphthous ulcers, leg edema, and diarrhea.¹⁶ Also, ADRs were observed between treatment groups. In the sirolimus group, 7 patients were lost to follow up due to ADRs compared to 1 patient in the control group.¹⁶

The authors noted the limitations to their study including small sample size (n=33) and the short study duration or 1 year.¹⁶ Also, the authors acknowledged that the high dropout rate in the sirolimus group was a weakness of the study. It is also speculated that those on azathioprine who converted to sirolimus may have seen a benefit due to the discontinuation of azathioprine rather than the initiation of sirolimus. The study concludes that sirolimus may be an option for renal transplant recipients with a history of NMSC, but larger multicenter studies are needed for further investigation.¹⁶
DISCUSSION

Renal transplant recipients have an increased incidence in post-transplant recipients, such as nonmelanoma skin cancer. Due to the anti-tumor effects of sirolimus, this may prove to be a valuable option as secondary prevention for renal transplant recipients with a history of NMSC. The above three studies\textsuperscript{14-16} demonstrated that a conversion to sirolimus reduced the incidence of NMSC in renal transplant patients with a history of NMSC. Furthermore, all studies\textsuperscript{14-16} were randomized control trials that demonstrated a reduced incidence of SCC lesions within the sirolimus treatment group. Sirolimus conversion led to a significantly lower rate of new NMSC lesions per patient year compared to the CNI group.\textsuperscript{14} Those patients who converted to sirolimus appeared to be survival free of SCC lesions significantly longer than those in the CNI group.\textsuperscript{14} Euvrard et al\textsuperscript{14} and Salgo et al\textsuperscript{16} observed an increased incidence of ADRs in the sirolimus group, while Campbell et al\textsuperscript{15} did not observe a significant difference in the incidence of ADRs between study groups. However, in Campbell et al\textsuperscript{15}, ADRs were the leading cause of discontinuation from the sirolimus group. This may be due to the difference in sirolimus conversion protocols between the studies.\textsuperscript{14-16}

While the evidence supports sirolimus conversion for immunosuppressive treatment in renal transplant recipients with a history of NMSC, there were limitations to these studies. Two studies\textsuperscript{14,15} lacked group allocation concealment and were open label studies, indicating that they were not blinded. The articles\textsuperscript{15,16} lacked precision due to lack of confidence intervals and use of p values for significance. Two studies\textsuperscript{14,15} demonstrated a high discontinuation rate in the sirolimus group due to adverse drug reactions. This resulted in small study populations and shortened study durations.\textsuperscript{14,15} For
example, Campbell et al\textsuperscript{15} calculated a sample size of 180 patients was needed for 90% power, but due to high discontinuation rates and low patient enrollment, only 86 patients were included in the study.

The quality of the data was further compromised with publication bias. Campbell et al\textsuperscript{15} demonstrated publication bias in their study. The study was sponsored by Wyeth Pharmaceuticals, a subsidiary of Pfizer Inc., who manufacture sirolimus. In Euvrard et al\textsuperscript{14}, Pfizer provided a research grant, but the study denies Pfizer having a role in the trial design or the collection and interpretation of data, which makes publication bias unlikely.

The overall quality of evidence using GRADE criteria\textsuperscript{13} was low. Due to reasons discussed above, Campbell et al\textsuperscript{15} was downgraded to very low quality. Two studies\textsuperscript{14,16} were downgraded to low quality. This includes Salgo et al\textsuperscript{16}, which was downgraded due to lack of precision and only utilizing secondary outcomes relevant to the clinical question.

Currently, more research is being conducted to further investigate the effects of sirolimus on NMSC in renal transplant recipients. More research is needed to determine if the beneficial effect of the conversion to sirolimus is due to sirolimus’ mechanism of action or to the discontinuation of the other immunosuppressant.\textsuperscript{16} The TUMORAPA study\textsuperscript{17} is an ongoing study comparing sirolimus conversion to CNIs in renal transplant recipients with SCC over a 5 year period. Further studies are needed to determine when sirolimus should be initiated in patients to prevent skin cancer and what the treatment duration should be. More research is needed to determine the cost effectiveness of sirolimus compared to other immunosuppressive therapy. Also, further studies investigating the long term treatment effects of sirolimus on mortality are needed.
CONCLUSION

Sirolimus was demonstrated to be efficacious in reducing the incidence of NMSC lesions in renal transplant recipients with a history of NMSC. While it appears that sirolimus has an integral role in secondary prevention of NMSC, the treatment does not appear to be well tolerated and has serious adverse drug events. Sirolimus is a valuable treatment option for renal transplant recipients with a history of NMSC, but it is not likely that sirolimus will replace standard immunosuppressive regimens, such as cyclosporine. Further research is needed to demonstrate the long term effects of sirolimus and its safety in renal transplant recipients.
References


### Table 1: GRADE Evidence Profile

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<th>No. of Studies</th>
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<td>1</td>
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<td>2.48&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup>Lack of blinding, lack of allocation concealment, and follow up was amended due to low enrollment and high discontinuation rates.

<sup>b</sup>Salgo et al study<sup>3</sup> was designed to have approximately 90% power with a sample size of 90 patients per study group. However, only a total of 86 patients were included in the study. The use of p values rather than confidence intervals for statistical significance contributed to the lack of precision.

<sup>c</sup>Lack of blinding, lack of allocation concealment, and follow up was amended due to low enrollment and high discontinuation rates.

<sup>d</sup>Campbell et al study<sup>2</sup> was sponsored by Pfizer.

<sup>e</sup>Yearly NMSC rate per patient year.

<sup>f</sup>Yearly NMSC rate per patient.

<sup>g</sup>Lack of blinding, lack of allocation concealment, and follow up was amended due to low enrollment and high discontinuation rates.

<sup>h</sup>Lack of blinding, lack of allocation concealment, and follow up was amended due to low enrollment and high discontinuation rates.

<sup>i</sup>Salgo et al study<sup>3</sup> had a small study population with a total of 120 patients. Also, 95% CI (0.32-0.98) demonstrates a wide confidence interval and decreased precision.

<sup>j</sup>Lack of blinding, lack of allocation concealment, and follow up was amended due to low enrollment and high discontinuation rates in the Campbell et al study<sup>1</sup> and Euvrard et al study<sup>2</sup>.

<sup>k</sup>Salgo et al study<sup>3</sup> was downgraded due to having only the secondary outcome having relevance to the clinical question.

<sup>l</sup>Small sample sizes demonstrated a lack of precision in all studies<sup>3,4</sup>. Campbell et al study<sup>2</sup> lacked confidence intervals and Euvrard et al study<sup>2</sup> had wide confidence intervals, which demonstrated a further lack of precision.