Project Description

Title

Feasibility and safety of topical Sirolimus in the prevention of skin cancer in solid organ transplant recipients

Protocol Name: TRANSIROTOP01

Advances in immunosuppressive therapies have markedly improved short-term outcomes for solid organ transplant recipients. However, the associated immunosuppression results in a major increase in the risk of keratinocyte cancer. Solid organ transplant recipients have one to 2 orders of magnitude higher risk and incidence ratio for developing squamous cell carcinomas (SCC) and basal cell carcinomas (BCC) [1,2]. This translates in solid organ recipients reaching incredible incidence rates for SCC at 379/1000 patient-year for heart transplant recipients [3] and current prevalence rate of 11% for SCC at any given time for kidney transplant recipients [4]. Similarly, BCCs also occur at a much higher rate and represent an additional burden. Similar observations can be made for early cancer such as Bowen's disease and intra-epidermal carcinoma as well as actinic keratosis. To a lesser degree solid organ transplant recipients have an increase in melanoma and Merkel cell carcinoma rates. Most importantly, BCCs and SCCs have a much more aggressive course. Aggressive cancers occur in 2% of heart and lung transplant recipients over 2 years [5]. This translates in 66 to 83-fold higher standardized mortality ratios regarding keratinocyte cancers as compared to the general population [6]. Overall it cannot be disputed that in solid organ transplant recipients, keratinocyte carcinomas are a major burden in terms of morbidity, mortality and cost.

Currently upon diagnosis of a keratinocyte cancer, surgical excision with adequate margin is the only treatment option. Unfortunately, additional preventive or adjuvant measures adopted so far, have been suboptimal. Common field therapy of photodamaged skin or actinic keratosis is often proposed to transplant patients. Photodynamic therapy has not shown a clear preventative role in SCC development [7,8] unless performed in unrealistic 4 weekly cycles [9]. Topical fluorouracil has similarly no benefit on SCC formation and prevention [10]. There is some controversy whether imiquimod or other immunotherapies should be used in transplant patients. Besides, their efficacy is essentially around actinic keratosis and basal cell carcinoma rather than squamous cell carcinoma.

Specific to the context of solid organ transplantation, oral chemopreventive regimens have also been trialled. Retinoid (acitretin) therapy is an additional adjuvant to prevent occurrence of new SCCs [11]. At doses reaching 25 to 30mg per day (0.3mg/kg) a benefit is noted with a 13% reduction in SCCs in treated groups as opposed to a 28% increase in placebo groups.

However side effects and withdrawal from trials are important (52%) [12]. In practical terms, higher doses of acitretin are difficult to achieve in solid organ recipients. Similarly, oral fluorouracil (capecitabine) has demonstrated its benefit in reducing SCC and BCC incidence by 3-fold as compared to the pre-treatment period [13,14]. However, 70% of patients experienced significant side effects and dose adjustment with interrupted cycles of therapy. More recently, nicotinamide has been proposed as a chemopreventive measure for keratinocyte cancers [15]. Although it has not formally proven to be effective in solid organ transplant recipients, given its innocuous nature it is widely prescribed.

Modulation of the immunosuppression was thought in the past as the best strategy to fight skin cancers. This was demonstrated using mTOR pathway inhibitors such as rapamycin (Sirolimus, Everolimus). Indeed, these molecules despite being immunosuppressive do not induce an increase in SCC or BCC incidence [16]. In patients with SCCs, changing calcineurin inhibitors to Sirolimus resulted in a nearly two-fold reduction in the risk of SCC [17-19]. Unfortunately, tolerance of Sirolimus is poor and approximately 50% of patients withdrew from the trial and 94% in the Sirolimus group reported at least one serious adverse event. In routine practice, oral Sirolimus is associated with a diverse range of serious side effects (acne, albuminuria, mouth ulceration, oedema, rash and pneumonitis) that remain difficult to manage and often necessitate withdrawal of the drug. Nonetheless, the benefit in skin cancer occurrence despite achieving significant levels of immunosuppression is intriguing leading to suggestions that Sirolimus might have specific anticancer properties. Indeed, past studies have shown the importance of the mTOR pathway activation in the keratinocyte proliferative response to UVB irradiation [20]. This activation as part of the AKT pathway is one of the main drivers of epidermal proliferation and is thought to have a cancer promotion effect on cells carrying oncogenic mutations [21]. In preclinical models of skin cancer, whether UV or chemically induced, rapamycin whether systemic or topically delivered significantly reduces SCC formation clearly demonstrating the anti-tumour effects of mTOR inhibitors outside the context of organ transplantation. This resulted in a significant increase in the time to first SCC. Importantly this remains true even if animals concomitantly receive cyclosporine [22]. Overall, there is good preclinical and clinical evidence that mTOR pathway inhibition is an excellent way to prevent skin cancer in solid organ transplant recipients.

To circumvent the side effects of systemic Sirolimus therapy, topical rapamycin has recently been adopted [23]. Indeed, in multiple case reports and case series and in a phase 2 randomized controlled trial that included a dose escalation, 0.2% Sirolimus applied topically has been found to be effective in treating tuberous sclerosis (disease in which there is an upstream mutation in the mTOR pathway) related angiofibromas. The Sirolimus preparation was applied twice daily for 12 weeks on the face. In terms of safety, half the randomized subjects were children, there were no serious adverse events and only mild skin dryness (65%) and mild irritation (50%) were noted as compared to placebo. These side effects were manageable with emollients. Moreover, systemic levels of Sirolimus were below 0.25ng/mL, well below the concentrations reached through oral delivery that can have toxicity (5-15ng/mL). A similar approach has recently been reported using a 1% topical preparation once daily for up to 9 months without any safety concern in a pediatric population[24]. In particular, blood concentrations remained undetectable (below 0.2ng/mL).

Keratinocyte carcinomas are a major burden and result in mortality and morbidity in organ transplant recipients, particularly in Queensland with a high background skin cancer rate. Rapamycin delivered orally has been proven to reduce the burden of skin cancer. It is however accompanied by significant toxicity. Topical rapamycin has been proven to be effective in reducing skin cancer burden in animal models. It is also proven in patients including children with tuberous sclerosis to be safe and easy to apply but has never been attempted on the skin of solid organ recipients to prevent skin cancer.

Hypothesis

In this study, we hypothesize that 1% topical Sirolimus is safe to use and effective in reducing the burden of skin cancer. We propose to conduct a pilot phase 2 randomized controlled study with paired observations to evaluate the use of topical Sirolimus in this indication.

Trial design

Eligible patients: we aim to recruit forty (40) solid organ transplant recipients during review at the Transplant Skin Clinic of the Princess Alexandra Hospital (PAH). Patients will be considered if (1) they received their transplanted organ more than 12 months previously and (2) they have experienced at least 5 SCC/BCCs in the past 5 years and have at least 5 keratotic lesions on the dorsum (back) of each forearm at inclusion. We will exclude patients who are receiving or have received Sirolimus orally, those who have received a topical field therapy (e.g. Efudex or Aldara) in the past 6 months or those who are medically unstable. We will also exclude patients if any cancer lesion requiring treatment, or any open wound, is detected on the areas to be treated and evaluated. In particular, the study will not exclude any other form of systemic preventive treatment such as acitretin or nicotinamide.

Study design: randomized placebo controlled trial with a self-control design. Patients will receive the intervention on the dorsum of one hand and wrist, and the placebo on the dorsum of the contralateral (opposite) hand and wrist chosen randomly.

Intervention: Sirolimus 1% in a gel mixing ethanol and carboxyvinyl polymer will be applied nightly for 12 weeks on the dorsum of one hand and wrist while the other hand and wrist receives the vehicle only. Patients will be followed for a total of 24 weeks from initiation of the intervention. Preparations, blinding and randomization will be performed within the PAH pharmacy where the Sirolimus or placebo will be randomly assigned to the dorsum of the right or left forearm. Gel tubes will be clearly labelled for right forearm and for left forearm in order to avoid confusion.

Outcome measures: The primary outcome measure is the change in the surface and number of keratotic lesions at each time-point, as compared to initiation day, on photographic images[25]. A secondary outcome measure is the development of a skin cancer requiring intervention. Finally, we will also note safety, tolerability and potential adverse events.

Evaluation will be performed at 0, 2, 4, 8 and 12 weeks of treatment and 24 weeks post treatment when, at each time point, the dorsum of both forearms will be photographed.
At the 2 and 12-week time points peripheral blood will be collected to measure and monitor (1) Sirolimus levels and (2) electrolytes and other blood components that may indicate alterations of kidney or liver function. At the end of the 24-week treatment period all participants will have two skin biopsies, one from the treated area of each forearm. This will check for the activity of the drug.

Power calculation: To observe a 30% reduction in keratotic number/surface with a power of 80% and at a significance level of 0.05, 29 patients are required to be tested. Obviously, this study is essentially a pilot to determine feasibility, tolerability and safety as a first step towards a larger study.

References

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