Review paper

Non-melanoma skin cancer outcomes in kidney transplant recipients converted from calcineurin inhibitors to mTOR inhibitors: a systematic review

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Abstract

Renal transplant recipients treated with calcineurin inhibitors (CNIs) are at a high risk of developing a skin cancer. Therefore, new therapeutic options such as inhibitors of the mammalian target of rapamycin (mTORi) have been studied to find treatment regimens decreasing the rate of skin cancers. This systematic review focuses on recent randomized controlled trials studying the impact of conversion from CNI to mTORi in renal transplant recipients on development of non-melanoma skin cancers (NMSC). Outcomes of analysed trials revealed that conversion from CNI to mTORi in post-transplant patients reduces the risk and delays the occurrence of NMSC. However, mTORi protective properties against NMSC are more effective in patients with a history of a single SCC compared with multiple SCCs. At the same time, conversion to mTORi is associated with more common discontinuations secondary to adverse events and also increased mortality. In conclusion, conversion to mTORi is protective against NMSC but given the high AE rates and therapy discontinuation there is a need to determine who would benefit from conversion and search for new treatment regimens including combination strategies with mTORi.

Key words: calcineurin inhibitor, mTOR inhibitor, skin cancer, transplantation.

Introduction

Introduction of modern, highly effective immunosuppressive agents in treatment of organ transplant recipients (OTRs) has led to a significant reduction in post-transplant rejection rates and improvement of graft survival. Current potent immunosuppressive drugs are relatively safe however not devoid of side effects. Malignancy represents a major burden in transplantation medicine. Due to impaired immunity, cancers are more aggressive and may result in serious morbidity or mortality.

Non-melanoma skin cancers (NMSC) are the most common malignancies in solid organ transplant recipients [1–6]. Incidence rates of post-transplantation NMSC are approximately 7% after 1 year and 10–45% after 10 years since organ transplantation [3]. Chronic immunosuppression is the main cause of malignancies, however the type and duration of immunosuppression is also of great importance. Other risk factors associated with

a higher incidence of NMSC are advanced age, male sex, fair skin phototype, skin cancers prior to transplantation, premalignant lesions, UV exposure, infections (HPV, EBV etc.) and also genetic disorders such as autosomal dominant polycystic kidney disease [4, 5]. Different treatment modalities can result in not only increased incidence of cancers but also impaired organ function, mainly kidney [7]. Unlike in the general population, the most common skin cancer in OTRs is cutaneous squamous cell carcinoma (cSCC) [4, 6]. Other malignancies also reported are: basal cell carcinoma (BCC), Kaposi sarcoma (KS), Merkel cell carcinoma (MCC) and malignant melanoma (MM). The risk of developing SCC in OTRs is increased by 65 to 250-fold compared to the general population [6].

Calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus (TAC), are effective immunosuppressants used in treatment and prophylaxis of graft rejection following organ transplantation which are well documented to contribute to an increased incidence of secondary skin

cancers [8–10]. Changes of treatment regimens including dose minimization and drug alterations seem to reduce development of skin cancers in OTRs. SRL and EVR are inhibitors of the mammalian target of rapamycin (mTORi) that were reported to have skin carcinoma preventive properties [11–17].

Aim

The aim of this review was to analyse the available medical literature on the incidence of skin cancers after conversion from CNIs to therapy with mTORi in kidney transplant recipients.

Material and methods

An extensive search in the literature was performed in line with the criteria published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18] guidelines by two investigators using Medline and Web of Science electronic databases. We used the following combination of searched key words: "sirolimus", "everolimus", "rapamycin", "conversion", "randomized controlled trials", "renal transplant" and "kidney transplant". Inclusion criteria: articles concerning incidence of NMSC among transplant recipients converted from CNIs to mTORi, adult patients, and no duplicated data in the study. Articles not including non-melanoma skin cancers, treatment regimen without conversion from CNIs to mTORi, children, reviews, case reports, clinical trials not being RCTs and personal experience summaries, studies not meeting the inclusion criteria of this study or in a language other than English were excluded. Relevant articles were screened by title and abstract, then

the full text was assessed for eligibility. The search was concluded in November 2021.

Results

The flow diagram of this study is presented in Figure 1 [18]. We identified 400 potential studies and publications, and then 58 were excluded for duplication, 317 were excluded after title and abstract screening, while 16 were excluded after full text screening. Furthermore, articles were excluded for not being randomized controlled trials, not providing information on incidence of NMSC, not including NMSC, review articles, case reports or animal studies. The final set included 9 articles. Key studies and findings are highlighted in Table 1.

Impact of immunosuppressive drugs on the molecular mechanism of skin cancer

Lifelong immunosuppression of patients who underwent organ transplant is the primary but not solitary reason for increased frequency of malignancies. It seems that pathogenesis of skin malignancies involves complex interactions between OTRs' genetic background, demographics, oncogenic viral co-infections, UV-induced effects and immunosuppressive agents [4, 8].

CNIs have been proven to induce initiation and promotion of skin cancers by their mechanism of action [19]. CsA seems to contribute to carcinogenesis and tumour progression by inhibition of calcineurin, resulting in activation of transcription factor 3 (ATF3). ATF3 belongs to the AP-1 family, which downregulates p53 expression by negative regulation of p53 messenger RNA expression [20, 21]. ATF3 was observed to increase formation of SCC in mice and in humans [20]. CsA causes also resistance to UV induced apoptosis and promotes growth factors [19, 22]. Moreover, UV light exposure is well known to be a major factor for SCC formation. Dziunycz *et al.* reported a synergistic effect of combined UV light and CsA treatment causing potentiated expression of ATF3 resulting in development of SCC in the sun-exposed areas of the OTRs' skin [22].

However, CNIs constitute a crucial treatment option in OTRs which prevents post-transplant rejection, various therapeutic options have been extensively studied to find treatment regimens decreasing the rate of skin cancer in this population. Among the most often studied are mTORi which possess both immunosuppressive and antitumor activity [23, 24].

SRL and EVR are macrolide antibiotics the pharmacokinetic and drug interaction profile of which is similar to CNIs (CsA, TAC), however they have immunosuppressive, antineoplastic and antifungal properties. mTORi act through the mechanism of inhibition of a serine-threonine kinase, mammalian target of rapamycin. Moreover, they block the response of T- and B-cell activation
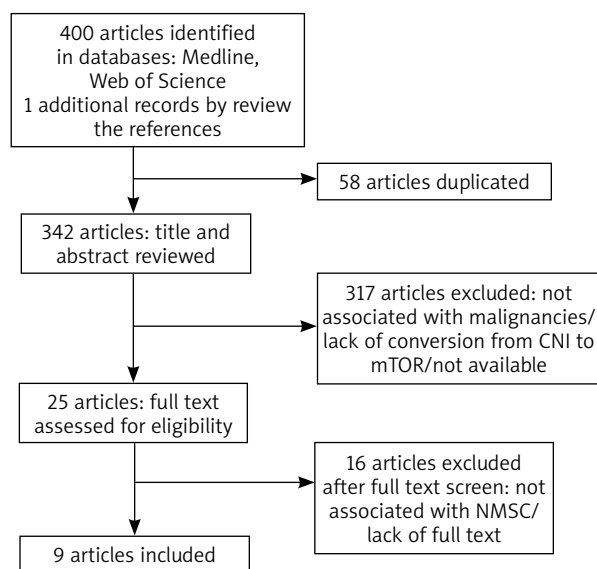

Figure 1. Flow diagram of the study according to PRISMA [18]

Table 1. Summary of published RCTs reporting the impact of conversion from calcineurin inhibitors to sirolimus/everolimus in renal transplant recipients on skin cancer incidence

Study	Year	Sample size	Main conclusions
Campistol [31]	2006	Renal transplant recipients ($n = 430$) SRL-CsA-ST ($n = 215$) SRL-ST ($n = 215$)	– Delayed median time to first skin cancer in the SRL-ST group (491 vs. 1126 d; log-rank test, $p = 0.007$) – Significantly lower risk for new skin carcinoma in the SRL-ST group compared to SRL-CsA-ST (0.346, 95% CI: 0.227–0.526; $p < 0.001$)
Salgo [17]	2010	Renal transplant recipients with premalignant skin lesions ($n = 44$) SRL ($n = 25$) Common therapy (CsA, TAC, azathioprine) ($n = 19$)	– Significantly more patients in the control group developed NMSC than in the SRL group (47.1% vs. 6.3%; $p = 0.0167$) – Better outcome of skin lesions in the SRL group at 12-month visit: no worsening of lesions, 73.4% were improved/control group: 70.6% worsening of lesions, lack of improved lesions
Euvrard [15]	2012	Renal transplant recipients with at least one invasive SCC ($n = 109$) CNI ($n = 56$) SRL ($n = 64$)	– SRL conversion group had a significantly longer survival free of new SCC than CNIs (HR = 0.37; 95% CI: 0.16–0.85), the difference remained significant for patients with single SCC but not for multiple SCCs – Higher rate of discontinuation and SAEs in rapid SRL conversion protocol vs. progressive SRL conversion protocol (30% vs. 15%; $p = 0.24$)
Campbell [16]	2012	Renal transplant recipients ($n = 86$) CNI ($n = 47$) SRL ($n = 39$)	– Lower rate of new NMSC per patient-year in the SRL group than the CNIs group (1.31 vs. 2.48, $p = 0.022$) – Significantly more patients in the SRL group were lesion-free compared to CNIs (43.6% vs. 19.1%; $p = 0.015$) – Prolonged median time to first NMSC lesion (380 days vs. 163 days)
Hoogendijk-van den Akker [11]	2013	Renal transplant recipients with at least one confirmed SCC ($n = 155$) SRL ($n = 74$) Other ($n = 81$)	– After 2 years, the risk reduction of new SCCs in the SRL group not significant in comparison to other regimens (HR = 0.76; 95% CI: 0.48–1.2; $p = 0.255$) – But at 1 year the HR was 0.50, significant 50% reduction in the SRL group
Alberu [12]	2011	Renal transplant recipients ($n = 830$) SRL ($n = 555$) CNIs ($n = 275$)	– Overall rate of malignancy was significantly lower in the SRL group than the CNIs group (2.1 vs. 6.0, respectively; $p < 0.001$) – Significantly lower rate of NMSC in the SRL than the CNIs group (1.2 vs. 4.3, $p < 0.001$) – Rate of all other malignancies did not differ significantly between SRL and CNIs group (1.0 SRL and 1.9 CNI group; $p = 0.088$)
Tedesco-Silva [30]	2016	Renal transplant recipients: ($n = 254$) evaluable for safety ($n = 195$) evaluable for efficacy analysis: SRL ($n = 86$) CMI (TAC) ($n = 109$)	– The SRL group had a lower rate of SCC of the skin compared to CNI (0% vs .5%; $p = 0.012$). – The number of patients with any malignancy did not differ between the groups (CNI 9 vs. SRL 4; $p = 0.158$)
Dantal [32]	2018	Renal transplant recipients with one SCC ($n = 120$) SRL ($n = 64$) CNI ($n = 56$)	– Survival free of SCC was significantly longer in the SRL than CNIs group ($p = 0.007$) – Survival free of SCC was significantly longer only for patients with one cutaneous SCC at randomization (crude HR = 0.20; 95% CI: 0.07–0.57; $p = 0.001$) – Number of patients with new skin cancers was significantly lower in the SRL than CNIs group (SCC: 22% vs. 59%; $p = 0.001$), other skin cancers: 34% vs. 66%; $p = 0.001$), and BCC (20% vs. 37.5%; $p = 0.05$) – At 5 years, conversion to SRL significantly reduces the risk of developing new cutaneous SCC compared with maintaining CNIs
Ying [33]	2018	Renal transplant recipients ($n = 192$) EVR + RD-CNI ($n = 131$) EVR + CNI-WD ($n = 68$) Controls: TAC/CsA + MPA + CS ($n = 87$)	– Comparison of 9-year risk of incident cancer/NMSC: – 15.6% of EVR patients developed NMSC compared with 19.5% in controls ($p = 0.4$) – EVR treatment was associated with a non-significant reduction in the risk of NMSC ($p = 0.1$) – Neither RD-CNI nor CNI-WD influenced overall cancer-risk after transplantation compared with controls (RD-CNI: $p = 0.9$, CNI-WD: $p = 0.4$) – Only EVR + RD-CNI showed a reduced risk of NMSC of around 56% vs. controls ($p = 0.02$)

CNIs – calcineurin inhibitors, RD-CNI – reduced-dose calcineurin inhibitors, CNI-WD – calcineurin inhibitors - withdrawal, TAC – tacrolimus, SRL – sirolimus, EVR – everolimus, SRL-CsA-ST – sirolimus-cyclosporine A-steroid, SRL-ST – sirolimus-steroid, MPA – mycophenolic acid.

by cytokines [24]. A few studies have reported a lower incidence of skin malignancies in transplant recipients treated with mTORi (Table 1). mTORi compared to CNI have a renoprotective effect, they cause less nephrotoxicity and prevent chronic allograft nephropathy [25, 26].

The differences between CNI and mTORi treatment results might be a matter of distinct impact on the function of regulatory T cells (Tregs) which are crucial for the induction and maintenance of peripheral tolerance. CNIs suppress both cytotoxic cells and Tregs functions, while mTORi seem to preserve the survival of Tregs resulting in tolerance towards alloantigens in organ transplant recipients [27]. Cegielska et al. observed that mTORi increase the level of Tregs in peripheral blood in kidney transplant recipients suggesting that mTORi allow to reduce the immunosuppression needed after organ transplantation [27].

On the other hand, mTORi are not deprived of adverse effects. Both adverse events (AEs) and serious adverse events (SAEs) have been observed after conversion to SRL/EVR. The leading AE include oral mucositis (aphthous ulcers), acneiform skin lesions, elevated transaminases, increase in triglycerides and cholesterol levels [28, 29]. Other frequent side effects are pneumonitis, proteinuria, diarrhoea and oedema [16, 17]. Moreover, patients converted to mTORi have relatively high discontinuation rates related to AEs but also higher rates of acute rejection compared to CNI.

Review of clinical trials

A summary of published studies reporting conversion from CNIs to SRL/EVR in kidney transplant recipients and its influence on skin cancers is presented briefly in Table 1. Multiple clinical trials presented a reduced risk of different types of NMSCs after CNI withdrawal and conversion to SRL/EVR after organ transplantation.

Campbell et al. performed a study that examined 86 transplant recipients with a history of NMSC that continued CNI (n = 47) or were converted to SRL (n = 39) [16]. The rate of new biopsy confirmed NMSC lesions per patient year was significantly lower in the SRL group than the CNI group (1.31 vs. 2.48, p = 0.022). The rates of new SCCs (0.88 vs. 1.77, p = 0.038) were also significantly lower in the group. However, in the BCC groups, no significant difference was found (0.43 vs. 0.77, p = 0.104) [16]. Discontinuation rates related to AEs were significantly higher for SRL than CNI (46.2% vs. 0%; p < 0.001) [16]. Of note, there was a high rate of study discontinuation in the SRL group (79%) while it was 49% in the control group.

Regarding efficacy of mTORi in skin cancer prevention, TUMORAPA trial by Euvrard et al. compared kidney transplant recipients on CNI therapy with patients who switched to SRL in terms of the anti-tumoral effect and history of previous invasive SCC [15]. The SRL group had

64 patients and 56 patients continued CNI therapy. Both groups had a history of a single cutaneous SCC (55% of patients of each group) and multiple lesions (45% of each group). The SRL group had a significantly longer survival free of cutaneous SCC than patients in the CNI group, with the hazard ratio for new SCC of 0.37 (95% confidence interval (CI): 0.16–0.85), and a study-adjusted hazard ratio of 0.38 (95% CI: 0.17–0.84) [15]. However, this difference remained significant only for the patients with a single SCC. Skin cancers developed in 20 patients in the SRL group and in 31 in the CNI group (47.6% vs. 70.5%, p = 0.048) [15]. AEs were more frequent in the SRL group than the CNI group and led to discontinuations in 15 (23%) patients after a median of 2.5 months. Interestingly, patients converted to SRL with rapid protocols had a higher rate of discontinuation than those who were converted with progressive protocols. Moreover, it seems that SRL antitumor properties are efficient when it is introduced after the occurrence of single, rather than multiple cutaneous SCCs [15].

Hoogendijk-van den Akker et al. also examined impact of conversion to SRL in renal transplant recipients on the incidence of SCCs [11]. The study group included 155 patients, 74 in the SRL group and 81 in the control group. Patients were converted from azathioprine, mycophenolate mofetil, CsA and/or TAC to SRL. In contrast to previous studies, Hoogendijk-van den Akker et al. demonstrated a statistically significantly lower rate of invasive SCC after 1 year of treatment (significant 50% risk reduction of a new SCC) (hazard ratio = 0.50 (95% CI: 0.28–0.90; p = 0.007)), while it failed to show benefits in terms of SCC-free survival at 2 years (non-significant 24% reduced risk), (hazard ratio = 0.76 (95% CI: 0.48–1.2; p = 0.255)) [11]. Moreover, SRL was especially effective during the first year after conversion in patients with only one previous SCC. Only one of 30 patients developed a new SCC 9 months after conversion in this group compared with 6 of 23 patients in the control group (p = 0.015) [11]. Twenty-nine (29) converted patients (39.1%) discontinued treatment because of AEs after a median time of 5.6 months. Interestingly, again SRL was proved to be much more effective during the first year with only one previous SCC compared with multiple SCCs before inclusion [11]. Those results are in line with Euvrard et al. study indicating that mTORi conversion is beneficial in patients with only one previous invasive SCC [15]. Moreover, increased incidence (39%) of AEs in patients converted to SRL was observed, compared to patients (2.5%) without conversion therapy. A high discontinuation rate was observed (42%) and it was similar to previous studies (24–35%) [15, 16].

A randomized controlled trial performed by Salgo et al. examined the impact of conversion to sirolimus on the rate of premalignant skin lesions and NMSC in renal transplant recipients [17]. The study examined 44 renal transplant patients who either continued previous im-

munosuppressive medication ($n = 19$) (azathioprine/my-cophenolate, CsA, TAC) or switched to SRL ($n = 25$) [17]. It showed that conversion to SRL in renal transplant patients inhibited the progression of premalignancies and significantly decreased the number of patients who developed histologically confirmed NMSC (6.3% vs. 47.1%; $p = 0.017$) during 1-year follow-up compared to the control group [17]. Interestingly, the SRL group showed a high discontinuation rate of 36% compared to 11% in the control group [17].

Since most of conducted trials had short follow-up, usually lasting 1 year, efficacy of antineoplastic properties of SRL were questionable in terms of lifetime therapy. Nevertheless, results of recent studies have resolved doubts. Some clinical trials examined malignancy rates in post-renal-transplantation maintenance therapy with a longer follow-up.

Tedesco-Silva et al. analysed patients after kidney transplantation with early conversion to SRL during 24 months [30]. As seen in other studies, conversion to SRL was associated with fewer cases of NMSC compared with CNI (TAC) continuation (0 vs. 6; $p = 0.012$) [30]. However, withdrawal from CNI and switch to SRL was associated with higher rates of biopsy-confirmed acute rejection (8% vs. 2%; $p = 0.02$) and discontinuation due to adverse events (21% vs 3%; p < 0.001) [30].

Hoogendijk-van den Akker et al. found that conversion to sirolimus resulted in a lower rate of SCC after 1 year of treatment but it failed to show beneficial outcomes after 2 years [11]. On the other hand, Alberu et al. study showed that patients undergoing SRL therapy had significantly lower rates of NMSC through 2 years post-conversion than the CNI group (1.2 vs. 4.3, $p < 0.001$). However, the rate of other cancers (excluding skin cancers) was not significantly different between treatment groups ($p = 0.058$) [12]. It seems that reduced rates of cancer after conversion from CNIs to SRL are driven by skin cancers rather than other cancers.

Another interesting trial by Campistol et al. compared two treatment groups that both contained SRL (SRL-CsA-steroid (ST) vs. SRL-ST after CsA withdrawal at month 3) over a longer period of time [31]. The median time to first skin carcinoma was delayed, moreover the risk of skin carcinoma was significantly lower with SRL-ST therapy (SRL-ST to SRL-CsA-ST 0.346; 95% confidence interval 0.227 to 0.526; $p < 0.001$, intention-to-treat analysis). The results showed also reduced incidence of non-skin malignancies (9.6% vs. 4.0%; $p = 0.032$) and a significantly lower risk for an event at 5 years after renal transplantation compared with those who received SRL therapy combined with CsA (relative risk SRL-ST to SRL-CsA-ST 0.346; 95% confidence interval 0.227 to 0.526; $p < 0.001$) [31].

The research results of Dantal et al. who extended at 5 years the TUMORAPA randomized trial are very promising in terms of long-time therapy [15, 32]. Dantal et al. study proved that conversion to SRL significantly decreases the risk of cutaneous carcinomas (not only SCC) and the beneficial effect is maintained at 5 years [32]. The number of patients with new skin cancers was significantly lower in the SRL group compared with the CNI group: 22% vs. 59% for SCC ($p < 0.001$), 34% vs. 66% for other skin cancers ($p < 0.001$), and 20% vs. 37.5% for basal cell carcinomas ($p < 0.05$) [32]. Moreover, survival free of cutaneous SCC was significantly longer in the SRL group than in the CNI group ($p = 0.007$) [32]. However, this result remained statistically significant only among patients with a single SCC before randomization, which is in line with other randomized controlled trials [11, 15, 16]. AEs were frequent, similarly to previous studies. Almost all patients had drug-related AEs that led to discontinuation in 23% of patients within 2 years and additionally 11% of patients between 2 and 5 year of trial [32]. The rate of discontinuation was similar to other studies [11, 16]. No episode of acute rejection occurred in the SRL group and the renal function was stable during the trial [32]. Both Campistol and Dantal et al. studies showed long-term anti-tumoral effect of conversion from CNIs to SRL that was maintained at 5 years [31, 32].

A recent study by Ying et al. for the first time compared such a long-term risk (9-years) of cancer, NMSC incident and death attributed to cancer among kidney transplant recipients [33]. Patients were randomized to de novo, early conversion EVR regimen or CNI-based triple therapy. EVR use was not associated with a reduction in the 9-year risk of incident cancer or cancer-related death compared with standard CNI-based therapy. Incidents of cancer were similar in both groups, 51 (26.6%) in the everolimus group and 21 (24.1%) in the control group ($p = 0.6$) [33]. Moreover, the proportion of cancer deaths between EVR and control patients was similar (everolimus = 4.7%, control = 3.4%; $p = 1.0$) [33]. Interestingly, compared to controls only patients randomized to everolimus + reduced-dose calcineurin-inhibitor showed a 56% reduction for NMSC (unadjusted HR = 0.44 (0.21–0.92)), which remained significant after adjusting for age, gender and smoking (adjusted HR 0.45 (0.21–0.96)) [33]. The reduction in the risk of NMSC was not seen in the CNI-withdrawal group. Unlike previous studies, Ying et al. showed that a combination of mTOR inhibitor and CNI in a reduced dose is beneficial in terms of the long-term risk of NMSC compared to mTOR and CNI withdrawal.

Disadvantages of conversion from CNIs to SRL/EVR in OTRs

A regimen of SRL alone may be advantageous for decreased incidence of skin malignancies however multiple studies reported the low allograft survival, more common SAEs and higher mortality rate related to mTORi conversion [34–38].

Knoll et al. meta-analysis of 5876 kidney transplant recipients from 21 randomized trials confirmed that SRL

was associated with reduction in the risk of NMSC (56%) and all types of malignancy (40%) [34]. The large study group enabled to detect that SRL was associated with an increased risk of death, both in the conversion ($p < 0.001$) and de novo trials ($p = 0.003$) [34].

Another large longitudinal cohort study analysing data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry, included 9353 adult patients who underwent kidney transplants, and confirmed a higher mortality risk with the use of mTORi while the treatment was not significantly associated with the risk of graft loss [35]. Meta-analysis of 29 randomized trials, likewise, demonstrated that discontinuation secondary to AEs was more common in patients on mTORi than on CNI (21.6% vs. 9.6%, $p = 0.020$) [38]. Moreover, patients converted to mTORi had a higher risk of acute rejection within the first year following the conversion ($p = 0.330$) [38].

The increased mortality observed in multiple studies [34–37] seems to diminish the decreased risk of cancer incidence during mTORi therapy. The results point out a need for a review of indications for CNI elimination and conversion to mTORi in transplant recipients. When it comes to a high rate of graft rejection and discontinuation of treatment due to AEs related to mTORi conversion, Tedesco Silva *et al.* study showed that EVR with reduced CsA might be a remedy [39]. Such treatment combination enables reduction of the CNI dose resulting in lower nephrotoxicity, NMSC incident and graft dysfunction but also minimizes the risk of graft rejection observed in conversion to mTORi. Tedesco Silva *et al.* proved that EVR plus reduced-exposure CsA is as effective as mycophenolic acid (MPA) plus standard-exposure CsA in terms of safety and efficacy but also the incidence of AEs is comparable [39].

Summary

Multiple studies have shown that conversion to mTORi from CNI in post-renal transplantation patients reduces the risk and delays the occurrence of NMSC. However, mTORi seems not to be a remedy in every case. Unless, the conversion of mTORi occurs after an initial diagnosis of a single cutaneous SCC it fails to show benefits in terms of multiple SCCs. Moreover, reduced rates of cancer were observed in skin malignancies rather than other cancers. Short follow-up of initial trials with SRL raised the subject of its efficacy in long-time therapy, however recent studies have confirmed that SRL beneficial effects were maintained even at 5 years. In spite of mTORi anti-tumoral effects, conversion to SRL seems to be associated with many disadvantages. In comparison to CNI, mTORi present increased incidence of AEs which usually lead to treatment drop out. Therefore, discontinuation rates are much higher in mTORi compared with CNIs. Despite a reduced risk of cancers, mTORi fail

to show improved patients' survival. A few recent studies highlighted the increased risk of death associated with SRL use which seems to diminish its beneficial effects as an immunosuppressive agent in transplant recipients. Nevertheless, majority of clinical trial results indicate a clinical benefit from the conversion to a mTORi-regimen in patients with low tumour burden in the early stage of disease. High AE rates and discontinuation of mTORi therapy results in search for alternative treatment strategies. Recent trials showed that efficacy and safety of EVR with a reduced dose CNI is comparable to standard treatment with CNI-MPA. Moreover, such treatment regimen resulted in reduction of the risk of developing NMSC, without the risk of graft rejection, therefore being a promising alternative to conversion from CNI to mTORi. It seems that further studies are needed to determine who would benefit from mTORi conversion or mTORi combined with reduced-dose CNI.

Conflict of interest

The authors declare no conflict of interest.

References

1. Collett D, Mumford L, Banner NR, et al. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. Am J Transplant 2010; 10: 1889-96.
2. Imko-Walczuk B, Dębska-Ślizień A, Szepietowski J, Rutkowski B. Problemy dermatologiczne chorych po przeszczepieniu narządów. Cornetis. Wrocław, Polska 2014.
3. Doshi MD. Cancer in Solid Organ Transplantation. In: Onco-Nephrology Curriculum. American Society of Nephrology Washington, D.C.: 2016; 11-92.
4. Mittal A, Colegio OR. Skin cancers in organ transplant recipients. Am J Transplant 2017; 17: 2509-30.
5. Jankowska M, Dębska-Ślizień A, Imko-Walczuk B, et al. Skin cancer in kidney transplant recipients affected with autosomal dominant polycystic kidney disease. Clin Transplant 2016; 30: 339-43.
6. Glover MT, Deeks JJ, Raftery MJ, et al. Immunosuppression and risk of non melanoma skin cancer in renal transplant recipients. Lancet 1997; 349: 398.
7. Porta C, Bamias A, Danesh FR, et al. KDIGO Controversies Conference on onco-nephrology: understanding kidney impairment and solid-organ malignancies, and managing kidney cancer. Kidney Int 2020; 98: 1108-19.
8. Cegielska A, Dębska-Ślizień A, Moszkowska G, et al. Association between HLA type and skin cancer in kidney transplant recipients. Transplant Proc 2016; 48: 1608-10.
9. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and anti-cancer effects of immunosuppressive agents used in organ transplantation. Transplantation 2004; 77: 1777-82.
10. Maluccio M, Sharma V, Lagman M, et al. Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. Transplantation 2003; 76: 597-602.
11. Hoogendijk-van den Akker JM, Harden PN, Hoitsma AJ, et al. Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutane-

ous invasive squamous cell carcinomas to sirolimus. J Clin Oncol 2013; 10: 1317-23.

12. Alberu J, Pascoe MD, Campistol JM, et al. Lower malignancy rates in renal allograft recipients converted to sirolimus-based, calcineurin inhibitor-free immunotherapy: 24-month results from the CONVERT trial. Transplantation 2011; 92: 303-10.

13. Mathew T, Kreis H, Friend P. Two-year incidence of malignancy in sirolimus-treated renal transplant recipients: results from five multicenter studies. Clin Transplant 2004; 18: 446-9.

14. Kauffman HM, Cherikh WS, Cheng Y, et al. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. Transplantation 2005; 80: 883-9.

15. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and secondary skin-cancer prevention in kidney transplantation. N Engl J Med 2012; 367: 329-39.

16. Campbell SB, Walker R, Tai SS, et al. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. Am J Transplant 2012; 12: 1146-56.

17. Salgo R, Gossmann J, Schofer H, et al. Switch to a sirolimus based immunosuppression in long-term renal transplant recipients: reduced rate of (pre-)malignancies and nonmelanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. Am J Transplant 2010; 10: 1385-93.

18. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006-12.

19. Athar M, Walsh SB, Kopelovich L, Elmets CA. Pathogenesis of nonmelanoma skin cancers in organ transplant recipients. Arch Biochem Biophys 2011; 508: 159-63.

20. Wu X, Nguyen BC, Dziunycz P, et al. Opposing roles for calcineurin and ATF3 in squamous skin cancer. Nature 2010; 465: 368-72.

21. Hofbauer G. Immunosuppressive therapy after transplantation. Dermatologic relevance and pathomechanisms. Hautarzt 2010; 61: 214-9.

22. Dziunycz PJ, Lefort K, Wu X, et al. The oncogene ATF3 is potentiated by cyclosporine A and ultraviolet light A. J Invest Dermatol 2014; 134: 1998-2004.

23. Geissler EK, Schlitt HJ, Thomas G. mTOR, cancer and transplantation. Am J Transplant 2008; 8: 2212-8.

24. Kahan BD. Sirolimus: a comprehensive review. Expert Opin Pharmacother 2001; 2: 1903-17.

25. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007; 357: 2562-75.

26. Tsai KF, Li LC, Hsu CN, et al. Effects of conversion from calcineurin inhibitors to sirolimus or everolimus on renal function and possible mechanisms in liver transplant recipients. J Clin Pharmacol 2019; 59: 326-34.

27. Cegielska A, Lisowska K, Dębska-Ślizień A, et al. Evaluation of quantitative changes in regulatory T cells in peripheral blood of kidney transplant recipients with skin cancer after conversion to mTOR inhibitors. Adv Dermatol Allergol 2018; 35: 474-80.

28. Guba M, Pratschke J, Hugo C, et al. Early conversion to a sirolimus-based, calcineurin-inhibitor-free immunosuppression in the SMART trial: observational results at 24 and 36 months after transplantation. Transpl Int 2012; 25: 416-23.

29. Yu JH, Kim KW, Kim BM, et al. Safety and immunologic benefits of conversion to sirolimus in kidney transplant recipients with long-term exposure to calcineurin inhibitors. Korean J Intern Med 2016; 31: 552-9.

30. Tedesco-Silva H, Peddi VR, Sánchez-Fructuoso A, et al. Open-label, randomized study of transition from tacrolimus to sirolimus immunosuppression in renal allograft recipients. Transplantation Direct 2016; 2: e69.

31. Campistol JM, Eris J, Oberbauer R, et al. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol 2006; 17: 581-9.

32. Dantal J, Morelon E, Rostaing L, et al. Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results. J Clin Oncol 2018; 36: 2612-20.

33. Ying T, Wong G, Lim W, et al. De novo or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: a trial-based linkage study. Am J Transplant 2018; 18: 2977-86.

34. Knoll GA, Kokolo MB, Mallick R, et al. Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. BMJ 2014; 349: g6679.

35. Badve SV, Pascoe EM, Burke M, et al. Mammalian target of rapamycin inhibitors and clinical outcomes in adult kidney transplant recipients. Clin J Am Soc Nephrol 2016; 11: 1845-55.

36. Cortazar F, Molnar MZ, Isakova T, et al. Clinical outcomes in kidney transplant recipients receiving long-term therapy with inhibitors of the mammalian target of rapamycin. Am J Transplant 2012; 12: 379-87.

37. Isakova T, Xie H, Messinger S, et al. Inhibitors of mTOR and risks of allograft failure and mortality in kidney transplantation. Am J Transplant 2013; 13: 100-10.

38. Lim WH, Eris J, Kanellis J, et al. A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. Am J Transplant 2014; 14: 2106-19.

39. Tedesco Silva H Jr, Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. Am J Transplant 2010; 10: 1401-13.