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Review

The change of immunosuppressive regimen from calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors and its effect on malignancy following heart transplantation

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ABSTRACT

Malignancy is a significant cause of mortality after organ transplantation. There is an increased rate of malignancy following heart transplantation (HTx) compared to the general population and other organ transplant recipients. Post-HTx patients with a history of malignancy are also at a higher risk of developing new malignancies or exacerbation of their existing malignancies. Mammalian target of Rapamycin inhibitors (mTORIs) are newly introduced immunosuppressive drugs with a unique mechanism of action. By changing the immunosuppressive regimen from classic drugs, especially calcineurin inhibitors (CNIs) to mTORIs, the rate of developing *de novo* malignancies and the relapse of former malignancies is significantly reduced. However, issues like allograft function, total surveillance of patients, and post-transplantation complications should be considered during the conversion of drug regimens utilizing CNIs to drug regimens employing mTORIs. We reviewed different post-heart transplant maintenance immunosuppressive regimens and their effect on post-HTx malignancies with a focus on mTORIs, compared safety against effectiveness, and gathered conclusions based on our review of the literature, which may lead clinicians to make a better evidence-based decision regarding post-HTx maintenance immunosuppressive drug regimens. Overall, CNI to mTORI conversion in post-HTx maintenance immunosuppressive drug regimens was associated with a reduced rate of developing malignancy in post-HTx patients. Furthermore, nephrotoxicity decreased significantly while using mTORIs in combination with lower doses of CNIs and the rejection rate was equivalent to CNI-only regimens. In conclusion, mTORI-based maintenance immunosuppressive drug regimens seem to be safe and beneficial when considering efficacy *vs.* adverse effects, and all-cause mortality rates are significantly lower in patients switched to mTORIs when compared to CNI recipients.

1. Introduction

Heart transplantation (HTx) is an established surgical treatment for patients with end-stage heart failure [1,2]. Patients experience improved quality of life after HTx [3]. Despite the extended survival and improved quality of life that this procedure offers to patients, there still exists controversy regarding the influence of different immunosuppressive drug regimens on patients' outcomes after HTx [4]. There are two important factors which impact our ability to improve long-term transplant results. The first factor is graft loss following chronic rejection of the transplanted organ, and the second factor is death with a healthy, functioning graft, which is commonly due to cardiovascular mortality or cancer [5].

Accordingly, a knowledge of mechanisms underlying cancer development resulting from the use of different drugs, and preparing the best immunosuppressive drug regimens that offer the maximum capacity for

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graft retention and reduction of life-threatening side effects to patients is very important.

The aim of this article is to review what we know about post-HTx malignancies and its relation to different immunosuppressive drug regimens, with a closer look at the proliferation signal inhibitor (PSI) family known as mammalian target of Rapamycin inhibitors (mTORIs), compare safety against effectiveness, and gather conclusions based on our review of the literature, which may guide physicians to make even better evidence-based decisions regarding post-HTx maintenance immunosuppressive drug regimens.

2. Epidemiology of cancer after heart transplantation

Malignancy is a major post-HTx complication [6,7]. The total incidence of malignancy is higher in the post-HTx population compared to the general population [2,5,8]. In some studies, the ratio of developing cancer has been reported to be 3- to 5-fold greater in post-HTx patients than the general population [9,10]. By studying 907 patients over an approximately 5.5-year time period, Roithmaeir et al. showed a 7.1-fold increase of developing malignancy in post-HTx patients compared to the general population [11]. The rate of developing malignancy is also higher in heart transplant recipients compared to other organ transplant recipients [12]. More than 10% of HTx patients develop malignancy between years 1 and 5 after the transplant, which causes a significant increase in the mortality of these patients [7].

Studies have shown that there are some differences in the tumor types between the general population and post-transplant patients [5], including post-HTx patients. According to a study conducted by Dona Mancini and Val Rakita, the most common cancer in non-transplant people is basal cell carcinoma (BCC), while most post-heart transplant patients develop squamous cell carcinoma (SCC) [13]. Post-transplant lymphoproliferative disease also occurs at a high rate [10,14]. Furthermore, there is a difference between the incidence of malignancy that develops in patients who have pre-transplant tumors and those who did not [15].

In 2000, Jensen et al. mentioned skin cancer as the most frequent malignancy in heart transplant recipients [16]. Following that report, many other studies have also reported SCC and Kaposi sarcoma (KS) as the most common malignancy in heart transplant recipients, with an incidence of about 42–50% [2,15,17–21]. Other involved organs that may develop malignancy include the lung, lymph nodes, bladder, colon, and stomach. The incidence of skin cancer, with the exception of lymphoma, increases with time after HTx [18].

3. Risk factors for cancer development after heart transplantation

Several factors play a role in the incidence of cancer following HTx. Some factors are common between these patients and the general population. It is known that advanced age [16], male sex, and being Caucasian are risk factors for developing cancer after HTx [18,22–25]. A positive history of pre-transplant cancer is another important factor. Such patients are at greater risk of recurring malignancy after HTx [6,15,23]. In a study conducted by Kang-Woo et al., cancer-free time was significantly lower among patients with a pre-transplant history of skin cancer compared to those without any history of malignancy before transplantation [26].

Immunosuppressive drugs can directly induce carcinogenic effects or cause conditions which make the body more susceptible to cancer, such as viral infections [27].

The intensity of immunosuppression and the increased activation of oncoviruses in immuno-compromised patients are important transplant-related factors, which increase the risk of developing cancer in HTx patients. These factors may be more pronounced in patients that have undergone heart transplantation when compared to many other organ transplant patients, because the immunosuppressive drug regimen after heart transplantation is more intense compared to the immunosuppressive drug regimens used after transplantation of different organs [8]. Interestingly, acute rejection may increase the risk of malignancy due to the patient's need for more aggressive immunosuppressive therapy [19].

Induction therapy, which consists of a specific immunosuppressant drug regimen to reduce the risk of acute rejection after HTx, may be another risk factor for the development of cancer [28]. However, the data describing the effects of induction therapy on the development of cancer are contradictory in nature. As an example, there are some studies, which have suggested that induction therapy is a risk factor for both skin cancer and other non-lymphoma type cancers [15,18,19], while in other studies, it has been reported that induction therapy for the prevention of acute transplant rejection does not seem to increase the risk of developing malignancy [22,23]. According to the Registry of the International Society for Heart and Lung Transplantation report in 2017, there was no difference in the rate of acute rejection between patients who received induction therapy and those who did not receive induction therapy [29]. Considering this issue, the author suggests that further studies are required to evaluate the effectiveness and safety of induction therapy for HTx patients.

There is some evidence suggesting that drugs used in maintenance immunosuppressive drug regimens can affect the rate of post-HTx cancer development and may represent one of the important risk factors for developing cancer. As reported in the literature, the most widely used drug regimen after HTx for maintenance immunosuppression therapy consists of an anti-proliferative agent [Mycophenolate mofetil (MMF) or rarely Azathioprine (AZA)], corticosteroids (prednisone or prednisolone), and a CNI [Cyclosporine A (CsA) or Tacrolimus], or a mTORI [Rapamycin or Everolimus (EVL)] [21]. However, recently, MMF or AZA has been replaced with mTORIs in maintenance drug therapy regimens for immunosuppression [4]. Recent studies have shown that AZA use is associated with an increased incidence of malignancy in post-HTx patients due to the direct effect of AZA impeding DNA repair mechanisms [8]. CsA and tacrolimus have also been associated with cancer progression in some studies [8,30,31]. Furthermore, long-term exposure to CsA is linked to an increased risk of SCC [6].

On the other hand, there are some drugs categorized as mTORIs that are unique immunosuppressive agents due to their anti-proliferative and anti-migratory actions, which appear to act independent of their normal modulation of B-cell and T-cell function. This mechanism may interfere with many proto-oncogenic pathways. The consequence of this effect is the anti-tumor properties of this family of drugs, which makes them remarkable when used in clinical practice [8,32].

Since it is currently known that there is a higher incidence of malignancy in post-HTx patients, possible strategies to prevent the development of cancer in this population should be considered. One method that might offer hope is to change the immunosuppressive drug therapy regimen from more conventional drugs with possible carcinogenic effects, especially CsA and tacrolimus, to mTORIs, which are discussed in this review.

4. Calcineurin inhibitors - mechanism of action in the development of malignancy

The mechanism of action of CNIs is involved in their carcinogenic effect. CNIs interfere with intracellular signaling pathways of T-cells and the result of this effect is the inhibition of the gene expression of inflammatory cytokines such as interleukin 2, 6, and transforming growth factor β (TGF-β) [5,33], although this process does not happen in tumor cells. For example, Weischer et al. noted that CsA increases the synthesis of inflammatory cytokines in tumor cells, especially TGF-β and VEGF (vascular endothelial growth factor), and can cause tumor growth, angiogenesis, and metastasis [33]. Additionally, CsA can exacerbate tumor growth in patients who already have pre-existing cancer [19].

These same results have also been observed with tacrolimus in other

studies [34–36]. However, it should be noted that tacrolimus promotes less tumor growth than CsA [8,30,31].

5. Mechanism of immunosuppression of mTOR inhibitors and their role in malignancy regression

Normal tissues have many methods to control their growth and development. Some of these methods affect cell cycle progression by either changing the activity of various enzymes, or releasing biochemicals. There are 3 phases in the cell cycle: G1, S, and G2. Each phase has its specific checkpoints that control entrance and exit to that phase. mTOR is a member of a newly identified family of phosphatidylinositol-3-kinases (PI3Ks) [8], which are involved in many critical regulatory cellular functions related to the cell cycle, such as cell cycle progression, cell cycle checkpoints that manage cellular responses to DNA damage, DNA repair, and DNA recombination. In addition, mTOR regulates essential signal transduction pathways and is involved in the coupling of growth stimuli with cell cycle progression [8,37].

The PI3K/Akt/mTOR pathway (Akt is Protein kinase B) is also important in tumor growth. Like normal cells, tumor cells not only use the mTOR pathway for growth, but also for the development of metastasis [5]. In tumor cells, the activation of mutations, amplification of oncogenes, and lack of tumor suppressors occur frequently in this pathway [38].

mTORIs, such as rapamycin, interrupt the PI3K/Akt/mTOR pathway, which plays a critical role in the regulation of proliferation, survival, mobility, and angiogenesis of tumor cells [5,8,12].

mTOR stimulants accelerate cell cycle progression and cell proliferation by increasing mRNA transcription in the G1 and S phases of the cell cycle. In contrast, mTORIs inhibit cell growth and proliferation by inhibiting the translation of critical mRNAs involved in the G1-to-S-phase transition in response to mitogenic stimuli (Fig. 1) [37]. Rapamycin can also induce selective apoptosis in those cells that are not functional and healthy, such as tumor cells [38].

Besides this direct effect, the use of mTORIs as substitutes for CNIs potentially affords a reduction in the adverse effects elicited by the CNIs, for example, the development of malignancy [12].

6. Pre-clinical evidence of the anti-tumor effect of mTOR inhibitors

Hojo et al. showed that CsA could promote neoplastic progression and metastasis when used in beige mice [39]. Maluccio et al. showed that a similar result occurred when using tacrolimus [34,35]. These studies have shown that overexpression of TGFβ was responsible for tumor invasion and metastasis [35,39]. Rapamycin, as the primary mTORI, was shown to have an inhibitory effect on cell proliferation and colony formation in a small cell lung cancer cell line [40].

Rapamycin alone, or combined with CsA, prevented metastatic tumor progression and prolonged the survival of mice inoculated with either mouse renal cell carcinoma or human T24 bladder cancer. This group of drugs has also been shown to reduce the number of human renal cell carcinoma metastasis in SCID mice, while CsA alone increased the number of metastases [23,30].

There was also a notable decrease in the metastatic area in rapamycin-treated mice compared to control mice. In contrast, CsA-treated mice had an increased area associated with tumor [30]. Because of the extreme dependency of tumor cells for specific nutrients and energy, it has been suggested that tumor cells might be more sensitive to rapamycin's effect than normal cells [41].

In a study by Schumacher et al., tacrolimus alone increased the growth of hepatocellular carcinoma cells *in vitro*, while using either tacrolimus in combination with rapamycin, or rapamycin alone, significantly inhibited cell growth and increased apoptosis in these cells.

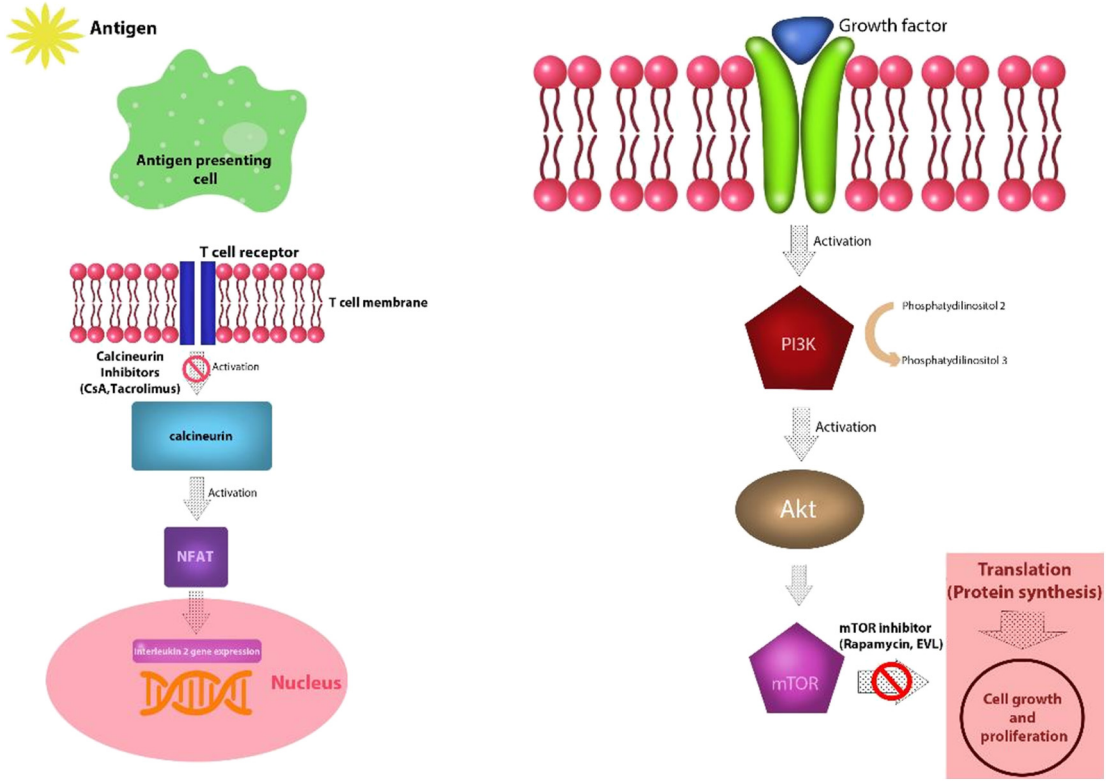

Fig. 1. The mechanism of immunosuppression with calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORIs). As illustrated, calcineurin inhibitors have no effect on cell proliferation process, while mTOR inhibitor's mechanism of action is directly relevant to their anti-tumor effects. The carcinogenic effects of calcineurin inhibitors are due to their different behavior in expression of cytokines in tumor cells compare to the normal cells. PI3K: phosphatidylinositol-3-kinases, Akt: Protein kinase B, mTOR: mammalian target of rapamycin, EVL: everolimus, CsA: cyclosporine A, NFAT: nuclear factor of activated T-cell.

Using rapamycin with tacrolimus was also observed to inhibit cell growth stimulation caused by tacrolimus. This result is especially important in those patients who require a stronger immunosuppressive regimen, for example, patients that have undergone liver and HTx [36].

Some *in vitro* studies have shown that rapamycin and EVL sensitize tumor cells to DNA-damage–induced apoptosis and support the idea of the anti-tumor activity of mTORIs [12,38].

Rapamycin can reduce tumor angiogenesis by inhibiting the proliferation of endothelial cells *via* the VEGF pathway [38,42].

Thus, mTORIs can decrease the risk of development of malignancy and its progression by several mechanisms, and this fact alone makes them a useful group of drugs for immunosuppression, especially in view of fact that they are associated with fewer adverse effects.

7. Clinical evidence of malignancy reduction by mTOR inhibitors after heart transplantation

It has been proven that rapamycin has a remarkable anti-cancer effect both *in vitro* and *in vivo* [43]. Because of the strong *in vitro* evidence supporting the anti-tumor effects of mTORIs, there have been many clinical trials using these drugs as a part of a maintenance immunosuppressive drug regimen in post-transplant patients. Most of these studies have been conducted on post-kidney transplant patients. These investigations have shown that the conversion of a patient's regimen from CNIs to rapamycin was associated with a lower incidence of SCC [44,45] and KS [5,6,43,46–48]. However, following this conversion, some patients failed to achieve optimum results due to the patient's existing condition (*e.g.*, extensive lesions or concomitant malignancies) [47,49].

There are several studies conducted on post-renal transplant patients, indicating the beneficial results of maintenance therapy with mTORIs. For example, in a 5-year follow-up of post-renal transplant patients, the incidence of malignancy was significantly lower in a rapamycin-treated group of patients *versus* a CsA-treated group of patients. Two cases of complete regression of KS, in these post-renal transplant patients, were reported after conversion to an immunosuppressive drug regimen that included rapamycin. In this study, cancer-free time was approximately 2-fold greater in patients who received rapamycin alone compared with those patients who received rapamycin plus cyclosporine [5].

Despite these beneficial results observed following kidney transplantation, there are limited studies on the use of these drugs in post-HTx patients. To date, many studies have shown a remarkable decrease in post-HTx malignancy while using mTORIs as a part of their immunosuppressive drug regimen [2,24,25,30]. Results of relevant studies are summarized in Table 1. Below, we will discuss, in detail, some of the studies conducted on post-HTx patients.

In a study by Doesch et al. involving cardiac allograft recipients, patients treated with mTORIs developed malignancy significantly less than patients who received CsA or AZA (in older regimens) as a part of their immunosuppressive drug regimen ($P = 0.02$ for CsA or AZA recipients *vs.* $P < 0.0001$ for mTORIs recipients) [25]. Furthermore, conversion to a CsA-free immunosuppressive regimen right after initial diagnosis seemed to increase survival of patients who developed malignancy in the follow-up period ($P = 0.05$) [25]. However, no significant improvement was observed in the reduction of recurrent cutaneous malignancies in patients who were switched to a CNI-free immunosuppressive regimen ($P = 0.68$) [25]. This observation might be due to other risk factors, such as radiation and infection, which may increase the risk for the recurrence of skin cancer.

In a larger study on post-HTx patients, administration of either CsA ($P = 0.0195$) or AZA ($P = 0.0008$) was associated with a higher rate of developing malignancy, whereas administration of mTORIs was associated with a reduced risk of developing malignancy ($P < 0.0001$). In addition, there was a significant reduction in mortality due to the recurrence of cutaneous ($P = 0.006$) and non-cutaneous ($P = 0.001$) malignancies when patients were using mTORIs instead of CNIs in the immunosuppressive regimen [24].

Wang et al. showed that the addition of EVL to an immunosuppressive drug regimen in patients that were already using a CNI decreased the risk of developing malignancies when compared to the addition of MMF (1.80% *vs.* 9.91% of all malignancies) [2].

Euvrard et al. noted that the overall risk of developing malignancies is significantly lower in EVL recipients *versus* other groups ($P = 0.03$).

Additionally, Signorell et al. reported a significant reduction in the development and progression of skin cancers after converting the immunosuppressive drug regimen of a patient a 57-year old male HTx recipient from CNIs to mTORIs [31].

Finally, Kaboshiwaga et al. reported that among patients that underwent HTx, the rapamycin-treated group of patients had the lowest rate of cancer development among all agents used for immunosuppression (2/16 for the rapamycin-treated group *vs.* 14/16 for the other immunosuppressive agents) [21].

Of note, there are also conflicting results concerning the findings of the studies mentioned directly above, although the number of studies is limited. Karia et al., who studied post-transplant recipients, including HTx patients, reported a significant reduction in skin cancer risk in rapamycin-treated *vs.* non–rapamycin patients. However, the association between the use of rapamycin and the reduction of skin cancer did not reach significance [20], possibly due to the small number of HTx patients who received rapamycin.

In patients who develop *de novo* malignancies, reducing immunosuppression is associated with acute rejection and graft loss. In those cases, conversion to mTORIs may be a better way to achieve both graft retention and anti-oncogenic effects [6]. One possible mechanism associated with this desired outcome could potentially be that mTORIs reduce the growth of oncoviruses, such as the Epstein Barr virus (EBV). By decreasing the growth of oncoviruses, mTORIs have the potential to mediate regression of tumor growth in transplant recipients [50,51].

8. The efficacy of mTOR inhibitors *versus* CNIs in graft survival after heart transplantation

The issue of the effectiveness of an immunosuppressive regimen in preventing graft loss has been examined at two levels; specifically, 1) preventing acute rejection, and 2) maintenance of graft survival.

In the case of acute rejection, the number of studies available on the efficacy of mTORIs in graft survival after HTx is limited. Oberbaeur et al. assigned HTx patients to two groups and followed them for 48 months. The first group received a regimen of CsA + rapamycin and the other group received gradual withdrawal of CsA over the 48-month time period and increased doses of rapamycin. These investigators suggested that there was no significant difference in acute rejection and mortality between the two groups one year after HTx [52]. However, it should be mentioned that there are some studies, which have shown that acute rejection occurs more frequently in patients using mTORIs than in patients being treated with CNIs as a part of their immunosuppressive drug treatment regimen after HTx [50,53,54].

In the case of chronic rejection, many studies indicate that mTORIs could have a remarkable role in maintenance immunosuppressive drug regimens after HTx. Wang et al. suggested that EVL, as an mTORI, in combination with tacrolimus, which is a CNI, exhibited good efficacy and safety when used after HTx [55]. In another investigation conducted by Asleh et al. in 2018, it was found that there was no significant difference in graft rejection and function in a group of patients that received CNIs when compared to patients who received rapamycin instead of CNIs (left ventricular ejection fraction was used as the index for comparison) [56]. Wang et al. showed that a reduced dose of CsA, as a CNI, in combination with EVL, which is an mTORI, was successful in graft retention, as well as a regimen that consisted of high-dose CsA without EVL [57]. Andreassen et al. obtained the same results in their study [58]. In a study conducted by Korang et al., all patients who

Table 1
Studies evaluating the effect of mTORIs on the rate of cancer in post-Heart transplant patients.

Author, year of study	Study type	Follow up duration	No. of patients undergoing HTx	Transplanted organ	Induction therapy	Maintenance immunosuppressive regimen	Conversion result (increase/decrease cancer rate)	Most common cancer
Karia, 2016 [20]	Retrospective obs.	4 years	58	Heart	Not mentioned	AZA/MMF + CNIs/rapamycin + prednisolone	A significant reduction in skin cancer risk was observed in the rapamycin-treated *vs.* non-rapamycin group ([26.8%] *vs.* [38.4%]; $P = 0.045$) and among non-renal OTRs (of 152 non-renal patients, 58 patients underwent heart transplant) ([23.5%] *vs.* [39.3%], respectively). In HTx patients, the association between the use of rapamycin and reduction of skin cancer was not significant ($P = 0.09$).	SCC Head and neck cancers
Wang, 2016 [2]	Retrospective obs.	4.75 years	454	Heart	+	CNIs (cyclosporine/tacrolimus) + MMF/mTORI (EVL) + prednisolone	Addition of EVL to the regimen of patients using a CNI decreased the risk of developing malignancies compared to addition of MMF (1.80% *vs.* 9.91% of all malignancies). No significant difference in survival rate was found after developing malignancy in either groups ($P = 0.745$).	Lymphoma SCC Lung SCC
Rivinius et al., 2015 [24]	Retrospective obs.	9.7 years	381	Heart	+	CsA/mTORIs + AZA/MMF + corticosteroids +	The administration of CsA ($P = 0.019$) was associated with a higher rate of developing malignancy while administration of mTORIs was associated with a reduced risk of developing malignancy ($P < 0.001$). The mortality due to the recurrence of the cutaneous ($P = 0.006$) and non-cutaneous ($P = 0.001$) malignancies was reduced when patients were using mTORIs instead of CNIs in the immunosuppressive regimen.	Skin cancers Non-cutaneous cancers
Doesh et al., 2010 [25]	Retrospective obs.	9.2 years	211	Heart	+	CsA/mTORIs + AZA/MMF + corticosteroids	Administration of CNIs for more than one year was associated with a higher ratio of developing malignancy ($P = 0.02$). Conversion to mTORIs significantly decreased the ratio of developing malignancy ($P = 0.0001$). No statistically significant change was observed in reduction of the recurrence of skin cancer after switching to a CNI-free regimen.	Skin cancers
Euvrard, 2009 [30]	Observational study		635	Heart	+	CsA/mTORI (EVL) ± AZA/MMF	Decreased overall rate of developing malignancy in the EVL *vs.* non-EVL groups ($P = 0.03$)	NMSC
Crespo-Leiro, 2008 [18]	Retrospective obs.	At least one year	3393	Heart	+ In 60.5% of patients	CNIs (cyclosporine or tacrolimus)/mTORIs + MMF/AZA + prednisolone	In a univariate analysis, tacrolimus use was associated with a reduced rate of skin cancer. However, in a multivariate analysis adjusting for some risk factors, the association between tacrolimus use in the first 3 months after transplantation and reduction of skin cancer was not significant anymore. The association between mTORIs and cancer was not reported.	Skin cancers mostly SCC
Signorell [31]	Case report	5	1	Heart	Not mentioned	CsA/mTORIs + AZA	A significant reduction in the development and progression of skin cancers was reported after conversion of CNIs to mTORIs.	Skin cancers

HTx: heart transplant, Obs: observational study, CNI: calcineurin inhibitor, mTORI: mammalian target of rapamycin inhibitors, MMF: mycophenolate mofetil, AZA: azathioprine, SCC: squamous cell carcinoma, OTR: organ transplant recipients, EVL: everolimus, CsA: cyclosporine A, NMSC: non-melanoma skin cancer.

underwent HTx maintained stable allograft function and exhibited no antibody-mediated rejection [59].

Based on a recent review conducted by Fine et al., mTORIs have appropriate safety and efficacy for use as a maintenance immunosuppressive drug regimen after HTx [50]. Of note, in all studies, there was an increase in allograft survival when using rapamycin in combination with CsA or tacrolimus, but not with a drug regimen totally free of CNIs [32,58,60]. Overall, a rapamycin-based immunosuppressive drug regimen seems to be safe and beneficial when considering efficacy and adverse effects, and the 'all-cause' mortality rate was significantly lower in patients that had been administered rapamycin compared to patients that had received CNIs [56,58,61].

Thus, as described in studies by Gonzalez et al. and Manito et al. [53,54], patients who undergo CNI to mTORI conversion should first be analyzed for any risk factors that would predict rejection. Then, based on the results of the risk assessment, mTORIs could either be used instead of CNIs, or, at a minimum, mTORIs could be added to an existing regimen of CNIs with simultaneous reduction in the dose of the CNIs. However, it is important to emphasize that CNI to mTORI conversion might be associated with a higher risk of adverse effects in patients with moderate to high risk factors for transplant rejection [54].

9. mTOR inhibitors *versus* other immunosuppressive drugs: potential benefits and therapeutic management of potential hazards

Renal dysfunction is a frequent cause of morbidity after a heart transplant [29,52]. Based on recent studies, conversion from a CNI-based drug regimen to mTORIs was associated with improvement in renal function in most cases, even for those who either had chronic renal dysfunction, or were on dialysis before transplantation [3,32,52,54,58,59,62–65]. The reason for this fact might be the lower CsA dose needed for an immunosuppressive effect with combination therapy [66]. Wang et al. confirmed this fact by studying patients who were categorized as having Stage 2 to Stage 4 chronic kidney disease. In that study, adding EVL, as an mTORI, to the maintenance immunosuppressive drug regimen after HTx, as well as reducing the CsA dose by 50%, was associated with an improvement in renal function [67]. The only study to yield conflicting results was an investigation conducted by Asleh et al. They evaluated patients who were converted from CNIs to rapamycin [56]. In this study, the eGFR and serum creatinine did not change significantly between the two groups described above [56]. Overall, the renoprotective advantage of mTORIs would strongly support their inclusion as part of a maintenance immunosuppressive drug regimen following HTx [29].

Cardiac allograft vasculopathy (CAV) is another serious problem after heart transplantation [56]. The results of many studies indicate that use of rapamycin instead of either MMF, or AZA, in maintenance immunosuppressive drug regimens reduces the rate of CAV progression [68–71]. Furthermore, conversion of CNIs to rapamycin or EVL reduces plaque progression and other adverse effects of CAV in post-HTx patients [61,65,72].

Another problem with mTORIs is impairment of wound healing due to their anti-proliferative effect [66,73]. There was a significant increase in wound complications between a rapamycin-treated group *versus* a MMF-treated group in a study conducted by Kuppahally et al. [74]. In a study by Kaboshwaga et al., a rapamycin-treated group of HTx patients had more complications associated with wound healing than a rapamycin-free group of HTx patients [21]. This same result was obtained in a study by Zuckerman et al. in patients who received EVL instead of tacrolimus as a part of their maintenance immunosuppressive drug regimen after HTx [75]. However, Putschoegl et al. suggests that potential impairment with wound healing is not so significant that it should preclude the use of mTORIs [76]. In addition, mTORIs are usually used as part of a maintenance immunosuppressive drug regimen, which begins when the wound is no longer classified as a fresh wound. Thus, wound healing complications are rarely an important clinical problem when using immunosuppressive drugs post-transplantation.

Diabetes mellitus Type 2 (T2DM) is another important complication after HTx [77]. Some studies have suggested that conversion from CNIs to mTORIs was associated with improving the glycemic profile of heart transplant recipients [78]. However, Murakami et al. reported that there was no significant difference between CNI- and mTORI-treated groups of patients when it came to developing T2DM post-transplantation [79]. In a study by Barlow et al., rapamycin caused dose-dependent hyperglycemia and short-term insulin resistance [80]. In addition, as reported by Kaboshiwaga et al., more patients needed to receive insulin therapy after rapamycin treatment [21]. It should be noted, however, that hyperglycemia is a manageable complication of lesser significance when compared to the numerous and life-saving benefits of mTORIs in transplant patients. In patients who benefit from the anti-cancer effects of rapamycin, hyperglycemia can be conveniently controlled with insulin therapy [81].

Another limitation associated with mTORIs is dyslipidemia and an increase in serum triglycerides. This has been shown to occur in patients treated with rapamycin as a part of their immunosuppressive drug regimen [56,59,62,63,82,83]. The incidence of dyslipidemia was reported in approximately 40–75% of all SRL recipients [83]. The reason for the development of dyslipidemia might be related to the mTOR pathway's effect on lipid absorption, metabolism, and storage in adipose tissue [83]. Interestingly, EVL has been shown to have less of an effect on a patient's lipid profile than rapamycin, and has even been shown to result in an increase in serum HDL levels [62,63]. According to these results, and considering the important role of hyperlipidemia in the pathogenesis of cardiovascular diseases and the accompanying increase in mortality, the use of mTORIs should be considered with some degree of caution. However, there are other reports and studies that show the beneficial effects of mTORIs in reducing cholesterol accumulation in atherosclerotic plaque due to activation of macrophage cholesterol efflux [83].

In addition to these data, there are other factors that require reflection and careful consideration. For example, it is reported that the anti-proliferative dose of mTORIs is much higher than the dose needed for its immunosuppressive effects. In fact, it is 7-fold greater for EVL administered orally [43]. It should be mentioned that this fact might be different between drugs in this class. In a study by Baur et al., rapamycin and EVL demonstrated reliable efficacy in preventing rejection, but the dose of CNI needed for immunosuppression, when used in combination with EVL, was less than the dose required when used with rapamycin [63]. Furthermore, and as mentioned above, EVL appeared to exert a smaller change to a patient's lipid profile than rapamycin and has even been reported to increase serum HDL [63].

10. Limitations

As a potential limitation, mTORIs are not yet approved by the U.S. FDA for use in post-HTx patients, and many clinicians still avoid them. In addition, the clinical evidence on the use of mTORIs in post-HTx patients is still very limited and, in fact, all data used for this review were collected from observational studies. Most of these studies have been conducted on data retrieved from hospital registry systems. It is challenging to compare the effect of different immunosuppressive drug regimens on the rate of cancer development using this data because of both the number and complexity of drug combinations used for immunosuppression following transplantation. Moreover, changes in the medication regimen of transplant patients who are not involved in a controlled trial may be made in order to achieve better responses to treatment or take advantage of new immunosuppressant drugs. Medical advances in both diagnosis and treatment may partially explain the better overall survival for HTx patients treated with mTORIs [2], which are newer drugs relative to the older CNIs. Hence, strong evidence-

based decisions concerning the protective effects of mTORIs for maintenance immunosuppressive drug therapy after HTx will require further experimental studies and clinical trials.

11. Conclusion

In this review, we conducted a literature search of published studies over the time period of 1996 to 2018 in an attempt to demonstrate the efficacy, safety, and 'malignancy developing reduction ratio' when converting post HTx patients from CNIs to mTORIs.

The anti-tumor effects of mTORIs have been documented in various reports. These reports have shown a lower incidence of malignancy in HTx patients who have been treated with mTORI-based immunosuppressive drug regimens compared to those who have received other immunosuppressive drug regimens [2,24,25,30]. This fact clearly reinforces the importance of the mTOR pathway to the growth and proliferation of tumor cells.

When a clinician wants to convert a maintenance immunosuppressive drug regimen from CNIs to mTORIs after HTx, there are two very important issues that need to be considered. The first issue is the effect of immunosuppressive drug conversion from CNIs to mTORIs on the risk of allograft rejection. The second issue of primary importance is post-transplant complications, especially nephrotoxicity, infection, and malignancy. In this review, we have focused on the development of malignancy following HTx and the impact that using mTOR inhibitors has on this issue.

There is an increased rate of development of malignancy in post-HTx patients when compared to the general population and other organ transplant recipients. Post-HTx patients with a history of malignancy are also at greater risk of developing either new malignancies, or experiencing a relapse of a previous malignancy. By converting classic immunosuppressive drug regimens from CNIs to mTORIs, the rate of *de novo* malignancies and relapsing malignancies is significantly reduced. However, acceptable graft function and monitoring of patients is warranted when using mTORIs in a CNI-free maintenance immunosuppressive drug regimen. Thus, we would suggest that patients who are candidates for treatment with mTORIs first be evaluated for their risk of rejection to facilitate an evidence-based decision with regard to appropriate pharmacotherapy. After careful assessment of the patient's rejection risk, mTORIs may be used in combination with more potent drugs like CNIs. With a combination regimen, patients may potentially benefit from not only the potent immunosuppressive effects and the ability to reduce the CNI dose required to prevent graft loss, but also the direct and indirect anti-tumor effects of mTORIs.

In this review, we have presented literature suggesting that a rapamycin-based immunosuppressive drug regimen is likely to be safe and beneficial when considering efficacy, adverse effects, and the 'all-cause' mortality rate [55–57,59–61]. However, a thoughtful and careful clinical assessment is imperative before converting a post-HTx patient's immunosuppressive drug regimen from CNIs to mTORIs as it pertains to allograft survival.

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Conflict of interests

The authors have no competing interests to declare.

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