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REVIEW

Practical recommendations for the early use of m-TOR inhibitors (sirolimus) in renal transplantation

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Summary

m-TOR inhibitors (e.g. sirolimus) are well-tolerated immunosuppressants used in renal transplantation for prophylaxis of organ rejection, and are associated with long-term graft survival. Early use of sirolimus is often advocated by clinicians, but this may be associated with a number of side-effects including impaired wound-healing, lymphoceles and delayed graft function. As transplant clinicians with experience in the use of sirolimus, we believe such side-effects can be limited by tailored clinical management. We present recommendations based on published literature and our clinical experience. Furthermore, guidance is provided on sirolimus use during surgery, both at transplantation and for subsequent operations.

Introduction

The immunosuppressant (IS) sirolimus (Rapamune®, Wyeth, Philadelphia, PA, USA), a mammalian target of rapamycin (mTOR) inhibitor, is used in renal transplantation for the prophylaxis of organ rejection [1–4]. The nephrotoxicity associated with calcineruin inhibitor (CNI) use in renal transplantation [5] is not seen when sirolimus is used as IS therapy in non-CNI regimens [6]. This nonnephrotoxic benefit coupled with good long-term outcomes [3] and an associated good cardiovascular risk profile [7] makes it a valuable IS treatment. Sirolimus is an important option in solid-organ transplantation and some clinicians advocate early use. Furthermore, sirolimus therapy after early cyclosporine withdrawal can reduce the risk of some malignancies after renal transplantation [8].

The early use of sirolimus in IS regimens can increase the incidence of postoperative issues, such as impaired wound-healing [9], and lymphoceles [10,11], and may extend the duration of delayed graft function (DGF) [12]. Furthermore, there are no studies to guide the use of sirolimus in transplant recipients who subsequently require emergency or elective surgery. As a group of practicing nephrologists and transplant surgeons, we believe that these postoperative side-effects can be minimized by implementing a number of practical steps. The aim of this article, therefore, was to provide recommendations, based on a detailed review of the literature and our own clinical experience, on the optimal use of sirolimus in renal transplant recipients. Guidelines on its use in elective and emergency surgeries are also suggested. To facilitate these aims, we have assessed risk factors

that should be considered before using sirolimus. While it is recognized that other mTOR inhibitors are available, most of the data and comment given in the article refers directly to sirolimus. It is possible, therefore, to extrapolate the guidance and recommendations given here for sirolimus to instances where other mTOR inhibitors have been used, and where similar side-effects have developed.

Impaired wound-healing

The presence of certain factors such as diabetes, malnourishment, or being on treatment with drugs such as steroids or chemotherapeutic agents are well known to negatively affect wound-healing [13]. The use of sirolimus in the presence of one or several of these factors may exacerbate the wound-healing process, and its use in patients presenting with these factors should be carefully considered. Indeed, increasingly, clinicians are tapering or even discontinuing the use of steroids in the early post-transplant period in order to improve patient outcomes [14].

Sirolimus itself is associated with impaired wound-healing in a dose-dependent manner [15]. Although impaired rates of wound-healing can result in a longer hospital stay, it is not known whether long-term outcomes are affected. The mechanism of action by which sirolimus impairs wound-healing has been investigated in rodent models, where inhibition of angiogenesis has been demonstrated. Sirolimus reduces expression of vascular endothelial growth factor (VEGF) and nitric oxide (NO) [9], and inhibits smooth muscle cells and fibroblast proliferation [16] and matrix deposition [17].

Many clinicians avoid using sirolimus during the first week post-transplantation in an effort to avoid impaired wound-healing. However, in cases where sirolimus is used from the start there are a number of practical steps that may limit impaired wound-healing.

Individual risk factor assessment

Clear risk factors – both modifiable and nonmodifiable – have been identified in wound-healing (Table 1) [11,15,18]. Of particular note is physical habitus where the odds ratio for developing wound-healing problems increases with a higher body mass index value (BMI) [15]. It is recommended, therefore, that each individual is assessed for these risks, and this should help to decide whether to proceed with sirolimus treatment. Any modifiable risk factor should be addressed, if possible. If a nonmodifiable risk factor is identified, a risk–benefit analysis should be performed and, if appropriate, an alternative treatment to sirolimus should be considered.

Table 1. Risk factors for side-effects associated with sirolimus. It is recommended that each patient is assessed for these risk factors before using sirolimus [data from references 11, 15 and 18].

Risk factors	Independent risk factor in impaired wound-healing	Lymphoceles
Nonmodifiable		
Age (of donor and/or recipient)	✔	✔
African-American	✔	✔
Modifiable		
Concomitant steroids	✔	✔
Overweight (BMI>26 kg/m^2)	✔	✔
Thymoglobulin induction	✔	
Anti-coagulants		✔

BMI, body mass index.

Avoid a high loading dose

While the advantages in terms of lowering the rate of acute rejection episodes is proven with higher loading doses of sirolimus [19], a cumulative sirolimus dose of >35 mg during the first 4 days post-transplantation has been identified as an independent risk factor for impaired wound-healing [15]. Therefore, avoiding a loading dose and initiating and maintaining sirolimus at 2–4 mg/day, with an increase in dose above this only if target levels are not reached by day 7, is recommended. Target trough levels with *de novo* use should be maintained between 5 and 10 ng/ml, depending on concomitant immunosuppressant therapy. Caution is warranted, though, in patients at high immunologic risk: it is essential that if the loading dose is reduced in these patients, there is adequate additional immunosuppressive coverage.

Steroid avoidance or minimization

Steroid use with sirolimus has a synergistic effect on impaired wound-healing [20], therefore limiting its use, or the avoidance of high doses of steroids, may improve wound-healing outcomes [18]. It is imperative, however, to avoid under-immunosuppression, and the combination of sirolimus with other IS treatments in steroid avoidance regimens is currently under active review.

Surgical intervention strategies

If using staples and sirolimus, consider leaving the staples in place for 3–4 weeks to help prevent skin dehiscence. Ensuring that the surgeon is aware of the plan to use sirolimus post-transplantation may encourage extreme care when the wound is surgically closed. Finally, the use of wound drainage may improve wound-healing

outcomes; drains should be left in place until the flow is at an acceptable level.

Lymphoceles

The use of sirolimus is associated with an increase in lymphocele development (Table 2) [10,11,15,18]. Following renal transplant, in the presence of sirolimus, there is inhibition of postsurgical adhesion. Furthermore, sirolimus can also impede lymphangiogenesis [21]. Consequently, lymph fluid is not contained within the lymph system, and lymphoceles form.

In cases where sirolimus is used *de novo*, there are a number of practical steps that can be taken to avoid, or at least limit, lymphoceles.

Individual risk factor assessment

Clear risk factors – both modifiable and nonmodifiable – have been identified in the development of lymphoceles (Table 1). It is recommended, therefore, that each individual is assessed for these risks, and a decision on whether to proceed with sirolimus treatment is taken based on this risk profile.

Avoid a high loading dose

In line with the advice to reduce impaired wound-healing, a high loading dose should be avoided.

Steroid avoidance or minimization

Inflammation can help with adherence. Limiting the use of steroids, which are anti-inflammatory and have a synergistic inhibitory effect with sirolimus on tissue healing, may reduce the risk of lymphocele formation [18]. Caution is needed, though, to avoid under-immunosuppression.

Prevention using drainage

Although drainage protocols across Europe and the Middle East are varied, the general view was that using drainage and keeping the drains in place until drainage is <50 ml/day for 2 consecutive days post-transplantation can, for some, decrease the risk of developing lymphoceles [22]. Careful ligation of lymphatic vessels and avoidance of extensive dissection is also advised.

Table 2. Incidence of lymphoceles seen in clinical trials with and without sirolimus (SRL) treatment.

Reference	Incidence of lymphoceles (%) with SRL	Incidence of lymphoceles (%) without SRL	Treatment arm comparison (*P* value)
Goel *et al.* [11]	45.5	24.7–33.9	$P = 0.014$
Langer *et al.* [10]	38.0	17.0	$P < 0.001$
Knight *et al.* [15]	38.0	18.0	$P < 0.01$
Rogers *et al.* [18]	16.0	5.5	$P < 0.002$

Management of lymphoceles

While the majority of lymphoceles are small and do not require treatment [10], some cases of lymphoceles do require treatment. Indeed, the proportion of lymphoceles that require treatment appears to be higher with sirolimus use compared with nonsirolimus use [10,11].

The recommendations presented here on how to manage this side-effect are not necessarily specific to sirolimus-induced lymphoceles, but are more general guidelines on lymphocele management. Following *de novo* use of sirolimus, clinical and laboratory parameters should be closely monitored, and if resources allow, routine ultrasound following transplant is recommended. If there is evidence of deteriorated renal function an ultrasound is strongly advised. In the presence of a fluid collection and confirmation of hydronephrosis, a puncture should be performed to allow complete drainage of the lymphocele.

Deteriorated renal function in the presence of a lymphocele, and without signs of urinary outflow obstruction, that is, without hydronephrosis, may require a diagnostic puncture. Renal biopsy may be considered to determine the worsening renal function, though such procedures can differ between practices. In all of the cases above, a sample of the fluid should be sent for laboratory and culture analysis to exclude other causes of fluid collections, for example, urinoma. Figure 1 summarizes these treatment management steps.

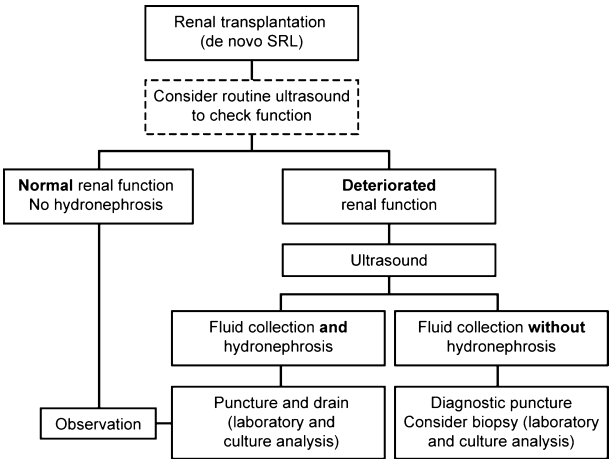

Figure 1 Algorithm for the management of lymphoceles following renal transplantation.

If the lymphocele is large and/or recurrent (with drain collection remaining above 500 ml/day), drainage via laparoscopic peritoneal window fenestration should be considered [23]. Drainage laparoscopically is also advised if a lymphocele re-fills following removal of the drain.

Delayed graft function

Delayed graft function (DGF) is defined as the need for dialysis within the first 7 days post-transplantation [24]. Following use of sirolimus in renal transplantation, DGF does appear to be extended; however, patient and graft survival do not appear to be affected following DGF associated with sirolimus. Whether or not sirolimus increases the incidence of DGF is not clear (Table 3) [12,25–30].

Acute tubular necrosis (ATN) is the histological diagnosis and principal cause of DGF. However, myoglobinuria and myoglobin casts have also been reported in four patients with sustained DGF (+14 days) among a series of 14 patients with myoglobin casts, and acute renal failure (ARF) was seen for 5–434 days post-transplantation in eight of these patients, all of whom were receiving sirolimus [31].

Patients at high risk of DGF include those receiving kidneys from marginal donors. CNIs are associated with nephrotoxicity, which can prolong recovery from DGF, so the use of these agents in such high-risk patients is under review [6]. Sirolimus has limited nephrotoxicity but it is important to balance this limitation with the risk of early side-effects.

Results from the landmark ELITE-Symphony study [30], using low-dose sirolimus (9 mg per day for 3 days, 3 mg per day thereafter and adjusted to achieve trough levels of 4–8 ng/ml) in combination with mycophenolate mofetil and corticosteroids significantly lowered the incidence of DGF compared with the low-dose tacrolimus group (21.1% of patients vs. 35.7%, $P = 0.001$).

Performing renal biopsy after transplantation can help to accurately diagnose ATN as a cause of DGF, and is useful to exclude other causes of nonfunction, such as superimposed acute rejection. In the case of ATN alone, it is recommended to wait for resolution.

There are a number of steps that physicians can take to limit DGF.

Individual risk factor assessment

Table 4 lists risk factors for DGF that should be considered before using sirolimus [32–37]. As with the previous side-effects, efforts to alter the modifiable risk factors should be made. Where risk factors are nonmodifiable, a risk–benefit assessment should be made before administration.

Table 4. Recipient and donor risk factors for delayed graft function.

Donor factors	Recipient factors
Age*‡§	Age*
Weight*	Weight*‡§
Cold ischemia times*‡§	Immunologic (HLA Mismatch >4‡, re-transplanted patients§)
Infections (Hepatitis C and CMV)§	Ethnicity§
Hemodynamic instability†	Previous dialysis*
Donor oliguria/anuria*	Gender (female)‡§
	Low blood pressure¶**

CMV, cytomegalovirus; HLA, human leukocyte antigen.
*Figueiredo *et al.* [32]; †Parzanese *et al.* [33]; ‡Carter *et al.* [34]; §Lebranchu *et al.* [35]; ¶Ozdemir *et al.* [36]; **Snoeijs *et al.* [37].

Table 3. Evidence of extended duration, but not incidence, of delayed graft function (DGF) with early sirolimus (SRL) use.

Reference	Treatment comparisons	Incidence of DGF	Prolongation of DGF	Patient and graft survival
Boratyńska *et al.* [25]	CsA-azathioprine-prednisone versus sirolimus-CsA-prednisone	Equal	Yes	Equal
Stallone *et al.* [26]	CS-CsA low-SRL versus CS-CsA full-MMF	Equal	Yes	Equal
Simon *et al.* [27]	SRL versus non-SRL	Increased	Yes	Equal
McTaggart *et al.* [12]	Steroid–MMF plus either: Depleting antibody; SRL; or neither	Not reported	Yes	Equal
Smith *et al.* [28]	Many	Increased	Yes	Not reported
Davis *et al.* [29]	SRL versus non-SRL	Increased	Yes	Not reported
Ekberg *et al.* [30]	Standard-dose CsA; Low-dose CsA; Low-dose tac; Low-dose SRL	Lowest in low-dose SRL group	Not reported	Equal for patient survival; lower allograft survival with low-dose SRL than low-dose tac

CsA, cyclosporine A; CS, corticosteroid; MMF, mycophenolate mofetil; tac, tacrolimus; SRL, sirolimus.

Avoid a high loading dose of sirolimus

As the degree (duration) of DGF associated with sirolimus appears to be dose-dependent, a high loading dose should be avoided and achieving a trough level of between 6–10 ng/ml is recommended.

Management of DGF

In the event of development of DGF during sirolimus treatment:
1 exclude acute rejection by performing transplant biopsies every 1–2 weeks during the period when DGF is noted to persist;
2 reduce sirolimus to a lower dose to achieve trough levels at 4–8 ng/ml;
3 consider temporary sirolimus withdrawal and switch to alternative combination therapy if DGF is severe;
4 re-start low dose sirolimus after 5–10 days, or once DGF is resolved.

Surgery in patients treated with sirolimus

In the years following renal transplantation, the need for surgery, either elective or emergent, is not uncommon. Indeed, surgery related to cancer in this setting may be increasing resulting from a combination of increased risk of malignancy in renal transplant patients and improvements in life expectancy [38]. One reflection of this is that cancer may surpass cardiovascular complications as the leading cause of mortality in transplant patients within the next 20 years [38].

There is currently little guidance on whether sirolimus treatment needs to be modified to avoid complications after elective or emergency surgery and if so, how to go about it. Figure 2 aims to provide some guidelines, based on our own clinical experience, of how to modify sirolimus use in case of minor, major (including surgical procedures for cancer) and emergent surgery.

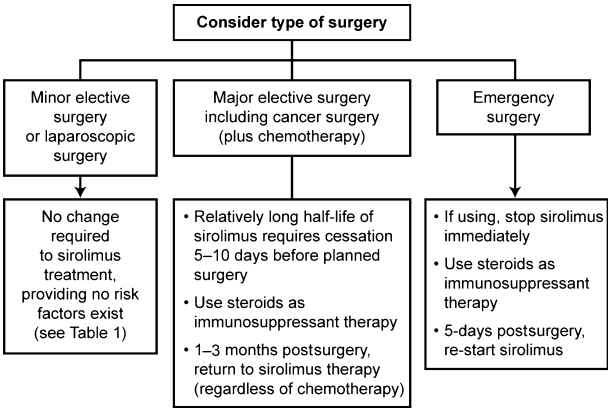

Figure 2 Guidelines on using sirolimus in the case of minor elective, major (including cancer) and emergency surgery.

Minor surgery

Simple uncomplicated wound-closures for skin and subcutaneous surgery, and surgery performed laparoscopically, are unlikely to be affected by the impaired wound-healing induced by sirolimus. It is recommended, therefore, that in this setting any current sirolimus treatment remains unchanged. However, if the patient has one or more of the risk factors identified for impaired wound-healing (Table 1), the advice would be to proceed with caution, and to consider lowering the dose in these particular patients. This approach is also recommended for hernia surgery, where healing of multiple tissue planes is required for successful repair.

Major surgery

The relatively long half-life of sirolimus necessitates that the drug is discontinued 5–10 days before planned major surgery in order to avoid any postsurgery complications such as impaired wound-healing, as described previously.

Steroid adjustment around surgery should follow standard published guidance in this area [39], or local protocols. If the patient is receiving a combination of sirolimus and mycophenolate without steroids, low dose steroid should be introduced following sirolimus discontinuation.

After surgery, we would recommend re-starting sirolimus treatment after 1–3 months, or when any courses of chemotherapy have finished.

Any deterioration in renal function should be promptly investigated and renal biopsies may be required to exclude an acute rejection episode in this setting. If there were to be a rejection episode in this setting, then treatment depending on the primary surgical problem will require to be carefully customized.

Emergency surgery

In the event of emergency surgery, sirolimus should be stopped as early as possible, again to limit any possible impaired wound-healing responses. As with major surgery, the use of steroids as immunosuppressants is recommended (Fig. 2). With respect to these recommendations, it may be noted that sirolimus could be re-started 5 days postsurgery: this should be sufficient time to avoid an impaired wound-healing response. In the case of emergent surgery necessitated by cancer, the line of recommendation set out for general major surgery from the point of differentiating cancer-related and cancer-

unrelated surgery can be followed, although it should be borne in mind that such circumstances will necessitate case-by-case considerations.

Conclusions

Sirolimus is an IS with a mode of action that differs from other IS treatments, and is associated with a low acute rejection rate, and good long-term outcomes [4]. A number of side-effects have been reported over the past decade following the early use of sirolimus in patients undergoing renal transplantation. A number of practical considerations are presented here that we believe can reduce these side-effects, and lead to better patient outcomes.

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