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Conversion to sirolimus

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INTRODUCTION

Two very relevant facts were observed from the first studies conducted with Rapamycin or Sirolimus (SRL) in renal transplantion (RT): 1) the virtual *absence of SRL-induced nephrotoxicity*[1] and 2) the *sinergistic effect of calcineurin inhibitor (CNI)-induced nephrotoxicity,* which complicates the association and forces, at the least, using lower doses of CNI if said association is sought. A third relevant fact observed in the first studies was the demonstration of an *immunosuppression potency similar to that of cyclosporine*[2,3]. These three facts made it necessary to present this drug as a very promising alternative to CNIs as a first level immunosuppressive drug in renal transplantion.

The use of SRL was considered from the beginning in two different scenarios in RT, a) from the first moment of the transplant *(de novo use)* in combination with or replacing CNI drugs, or b) in the stable transplant stage, generally replacing CNIs, which is what is referred to as *conversion use*, and the issue that will be discussed in this chapter.

This conversion in turn can be considered in two different circumstances: 1) as a procedure to try to correct or improve a problem that arises in the transplant patient, or 2) in a stable patient, who experiences no problems, in order to try to prevent long-term damage or toxicity induced by CNIs once the initial stage of higher immunological risk has passed. Until now the first option was used in almost all cases, although the second option is beginning to be more strongly considered[4].

The benefits of SRL that justify considering conversion in certain patients are two-fold: 1) on one hand, *elimination of the calcineurin inhibitor,* which would prevent or slow down the toxic effects resulting from it, and 2) on the other hand, the *specific additional effects of SRL,* especially the proven antiproliferative and antineoplastic effect thereof, which in some patients may become particularly important, as is the case of patients who develop malignancies.

In the initial stages, even before marketing of the product began (compassionate use), its use outside of clinical trials began as a conversion in patients with progressive allograft function impairment compatible with chronic allograft nephropathy (CAN), generally in very advanced stages of renal damage and with poor results. The lessons learned from these years have been geared towards correlating the benefit with the early conversion, as will be seen below.

The indications for conversion, as well as the most suitable time and the process for doing so, are not yet properly defined. There are still no large studies available that approach this issue, and there are only small series, generally single-center, with a rather small number of patients, most of them with retrospective analyses and no control group[5-10]. The only multicenter study conducted, which is a prospective and randomized conversion study of stable patients (CONVERT study, also known as study 316), including a total of 830 patients, has not yet been published and only preliminary results are available[11]. Nevertheless, experience in recent years has progressively defined some of these aspects such that most centers with more experience are progressively homogenizing their action guidelines, and this is what will be summarized in this chapter. A recent editorial by Diekmann and Campistol summarizes important issues on conversion in patients with CAN[12].

INDICATIONS FOR CONVERSION

Chronic Transplant Nephropathy / Calcineurin Inhibitor-Induced Nephrotoxicity

As stated in the foregoing section, the primary indication for conversion is the existence of CAN. This entity, which is the main cause of graft loss after the first year[13], is the consequence of a series of factors of an immunological origin (acute and chronic rejection) and non-immunological origin (donor age, ischemic damage/reperfusion, post-transplant high

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blood pressure, hyperlipidemia, drug-induced toxicity), which will not be discussed in this chapter[14], but in which calcineurin inhibitor-induced nephrotoxicity plays a relevant part[15,16] without any doubt today.

CAN is characterized by a slow but unyielding renal function impairment, leading to graft loss in quite a variable period of time. CAN is histologically scored according to the most used today Banff-97 classification, that includes interstitial fibrosis and tubular atrophy as the main findings, two completely unspecific lesions that do not allow distinguishing specific etiology[17], though other secondary lesions may be useful when distinguishing between CAN of an immune origin (chronic rejection) and non-immune origin. Today it is common knowledge that both renal function in early stages and the existence of histological CAN are obviously correlated with graft survival[18,19], but curiously enough there is a very poor correlation between these two factors[20,21], and it is generally accepted that renal function impairment is a later marker of renal damage, and that when it occurs, the possibilities of intervening are considerably reduced[22].

Although a series of factors related to the development of CAN are known, as seen in the foregoing section, the reason this process occurs in some patients but not in others is unknown. Once it occurs, the rate of progression of renal function impairment is also quite variable, and it may even remain stable for years in some patients with a histological diagnosis and renal function impairment.

The incorporation of SRL in the renal transplant therapeutic strategies soon revealed the possibilities of using it in patients with CAN for the purpose of eliminating the toxic effect of CNI, and its antiproliferative effect was secondly assessed for the purpose of delaying interstitial and vascular fibrosis associated with chronic allograft damage. SRL has shown its effectiveness in de novo clinical trials in *preventing CAN* either when it is administered without CNI from the first day of transplant[23] or when CNI is eliminated early on, as in trial 310[24,25] and in other similar smaller studies[26]. However, conclusive results showing an obvious benefit in *treating CAN,* i.e. stopping progression of the histological damage already established or even lesion regression, are not yet available. Most of the published series are focused on the evolution of renal function after conversion and other clinical and analytical parameters, but there are still no histological results. The CONVERT study (trial 316) mentioned above includes a histological study consisting of a baseline biopsy before randomization and a biopsy after two years to compare progression of the histological damage in both therapeutic groups, the SRL convert group and the CNI maintenance group, but these results are not yet available.

The published series on conversion in patients with CAN and/or calcineurin inhibitor-induced nephrotoxicity generally show a moderate post-conversion renal function improvement in a significant percentage of patients, but there is a patient subgroup in which renal function does not improve as was sought with the conversion, and it even worsens. For this reason it is important to be able to identify *a priori* which patients will benefit from this procedure and which will not, in order to make a better indication for the drug, i.e. it is necessary to identify those clinical or histological factors that may predict evolution after the conversion. Most of these series included patients converted with an already pronounced renal function impairment, and creatinine generally exceeds 2.5 mg/dL at the time of conversion (Domínguez: 2.8 mg/dL[27]; Egidi: 2.8 mg/dL[7]; Morelon: 2.7 mg/dL[28]; Diekmann: 2.9 mg/dL[29]; Renders: 2.4 mg/dL[30]; Wu: 2.9 mg/dL[9]). It can be seen in several of these series that the patient group in which renal function improves after conversion has a lower average *creatinine* than the group that does not improve or worsens. In this sense, in the Weber series the patient group with better renal function shows a higher percentage of patients with a good response (8). The Citterio series finds that the responding subgroup (renal function improvement) starts with lower creatinine than the non-responsive group[31], and Diekmann also shows similar data (creatinine at the time of conversion was 2.75 vs. 3.15 mg/dL respectively), although in this case there are no significant differences[29]. The preliminary results of study 316 also show a renal function improvement trend in the SRL convert group, but this improvement is not homogenous, and in fact the randomized patient group with a basal glomerular filtration rate between 20 and 40 mL/min shows worse renal function in the convert group with respect to the control group that maintained CNI. In fact an intermediate analysis of these results forced to modify the protocol so that patients with a creatinine clearance of less than 40 mL/min were not included in the study, supporting the results found in other small studies. In the randomized group with a basal filtration rate of over 40 mL/min a renal function improvement is observed in the convert group with a difference progressively increasing over time (2.7 mL/min filtration after a year and 3 mL/min after two years).

A second and increasingly important aspect when assessing the possibilities of post-conversion success is *baseline proteinuria,* especially since Diekmann's work[29]. A multivariate analysis assessing clinical parameters (age, sex, number of previous rejection episodes, creatinine and proteinuria) and histological parameters (CAN score according to Banff, presence of transplant glomerulopathy, percentage of sclerosed glomeruli and degree of vascular lesions) found that proteinuria at the time of conversion is the only independent predictive factor for a good response, establishing a cut-off at 800 mg/24 hours (90% positive predictive factor for a good response in patients with proteinuria under this limit)[29]. A correlation between baseline proteinuria and evolution of renal function can also be seen in study 316, so that the greater benefit is seen in patients who do not have proteinuria or in those in whom it is mild (less than 110 mg of proteinuria/g of creatinine)[11]. This factor, baseline proteinuria, probably indicates nothing more than the extent or severity of the chronic graft damage.

In the third place there are several works showing a correlation between *histological damage* and response, and generally there is a better prognosis in patients with milder histological damage. Diekmann found in the univariate analysis that the group with a good response has a lower CAN score (1.2 vs. 1.9; $p<0.01$) and less intimal thickening in vessels (1.2 vs. 1.7; $p=0.048$)[29]. In this sense, Weber observed that when specific chronic rejection lesions (typical vascular lesions) exist in the CAN context, the response is better than when there are no specific lesions, and only interstitial fibrosis and tubular atrophy are identified as CAN indicators, probably reflecting a different population[8]. This data is particularly interesting because the existence of lesions suggesting chronic rejection (i.e. an immunological origin of CAN) would be *a priori* data that would imply a worse post-conversion evolution, but however this is not the case.

An important aspect that should be discussed in this section is the use of SRL in conversion in patients receiving other solid organs who develop progressive renal failure impairment, which most of the time is the result of the toxic effect of the use of CNI over a period of years[32,33]. This is a growing problem as the population of long-term recipients of other solid organs increases, and it is a significant cause in starting dialysis today. SRL is progressively being included in the therapeutic approach, especially in patients receiving transplants who already present renal failure («de novo» use) and in those who develop progressive renal function impairment due to nephrotoxicity, with encouraging results[34-36]. The advantage of this model is that since there is no immunological damage to the kidneys themselves, it is easier to assess the effect of the conversion on renal function. As stated above, early intervention in renal transplant also seems to be a predictive factor for a good post-conversion response[34,37], so it should be considered in the initial stages of renal function impairment.

In summary, it seems clear today that the success of intervention with SRL in patients with CAN depends on two factors: 1) early intervention before irreversible damage spreads excessively, and 2) a procedure minimizing the risk of complications as much as possible, especially those resulting from overimmunosuppression, as will be seen below (regarding how to conduct the conversion and target levels). However this early intervention should not be based exclusively on increased creatinine levels, since it is most likely that when these levels appear it is too late; it should be based more on the closer assessment of changes in the glomerular filtration rate and in the early indication for an allograft biopsy, which allows identifying earlier lesions that have greater possibilities of being controlled. Diekmann and Campistol recommend converting patients with less than 2.5 mg/dL of creatinine[12], which seems to be a reasonable limit in light of current experience, meaning that patients having a higher creatinine level should not be converted, but in most patients it is important not to wait to reach these limits. Rather, a proactive attitude in searching for those patients who already show initial progression, should allow for a much earlier intervention.

In following with this line of early intervention, the protocol biopsy could be considered at a specific time after the transplant as a reasonable option, at least in select centers, for trying to identify those patients who are already developing certain chronic damage and who could especially benefit from the use of SRL, even though renal function at that time is «normal». This biopsy should probably be conducted between 3 and 12 months after the transplant[21].

Malignancies

The development of malignant neoplasias during the stable transplant stage has become a very significant problem over the years that influences patient survival and also graft survival due to changes in immunosuppression that must be carried out[38]. This problem has been known since the beginning of the transplant, but its importance has

grown progressively based on two fundamental factors: greater immunosuppression potency of new drugs and the older age of the patients, making susceptibility to developing neoplasias higher (as occurs in the general population)[39-41]. CNI drugs have a clear potentiating effect on the development of neoplasias and this effect seems to be related to stimulation of the synthesis of proneoplastic cytokines, such as TGFb and VEGF (vascular endothelial growth factor), and to the inhibition of apoptosis. In contrast SRL blocks the synthesis of these two mediators and this is probably related to its opposite effect with respect to tumor growth and its metastatic spread[42].

This is consistent with the results of clinical trials in which the use of SRL rather than CNI is associated with a lower incidence of neoplasias, but also even when it is administered in association with CNI (partly making up for the negative effect of the latter)[43,44]. In this sense, in 2004 Mathew published a joint analysis of 5 randomized clinical trials with different combinations of SRL and CNI, demonstrating a lower incidence of malignant neoplasias two years after the transplant in patients who received SRL without CNI (0% *vs* 5%), and also a lower incidence of cutaneous neoplasias in those who received SRL in combination with CNI in comparison with those who received CNI together with a placebo. The intermediate situation between these two opposing strategies, which would be the joint administration of SRL and CNI during the initial stages with an early withdrawal of CNI (trial 310), was also associated with a lower incidence of neoplasias than when CsA was maintained[45,46]. A recent publication analyzes the incidence of malignant neoplasias in the Organ Procurement and Transplantation Network (OPTN) register and compares this data among the patients who received SRL or Everolimus, Cyclosporine or Tacrolimus or combinations of the two groups (mTOR and CNI) in a series of over 33,000 transplants since 1996. The results show that the administration of an mTOR (alone or in combination with a CNI) is associated to a relative risk of developing a malignant neoplasia de novo of less than 0.5 (0.39 for any type of neoplasia and 0.44 for solid organ neoplasias) if considering that the risk is 1 when CNI is administered[47].

However even though today it is accepted that the use of SRL reduces the incidence of malignant neoplasias de novo after the transplant, detailed information on the effect of the addition of SRL or the conversion in patients who have already developed neoplasia after the transplant is not known. In this sense there are works showing an evident beneficial effect of converting to SRL on the evolution of certain malignant neoplasias, Kaposi's sarcoma being the clearest case in this sense[48-51]. In 2003, Campistol published the experience of two patients with Kaposi's sarcoma (with no visceral involvement) who were converted to SRL with complete remission of the tumor lesions in the following months and maintained stable renal function at all times[48]. Stallone subsequently published a series of 15 patients in whom a very similar response is shown after conversion. This author additionally demonstrates very high expression in tumor tissue of VEGF, the protein Flk-1/KDR and phosphorylated Akt kinase and p70S6, two enzymes of the metabolic pathway in which SRL intervenes, which could explain the beneficial effect of SRL in the evolution of this tumor[49].

In the case of post-transplant lymphoproliferative disease (PTLD), there are also published cases of good response after conversion to SRL as a single measure[52] or associated to treatment with Rituximab[53,54], although there is less experience in this type of tumor.

Occupying third place would be cutaneous tumors in which there seems to have been a clear relationship between conversion to SRL and a beneficial response for the tumor. Although there are no published works to this respect, there are several ongoing studies with promising initial results. These tumors, which are often cured with simple excision, are characterized by frequent relapses. In this case, conversion to SRL could prevent the occurrence of new tumors in a patient with a first diagnosed cutaneous neoplasia. This practice (secondary prevention) is reasonable and is used in a considerable number of centers today, although confirmation with randomized study results will contribute to consolidating it[55].

The classic strategy for controlling a neoplasia that develops after transplantation consists of a significant immunosuppression reduction (by associating or not associating a specific treatment to the neoplasia according to the type). This strategy should include at least eliminating antimetabolites and minimizing CNI, which obviously implies the risk of increasing the immunological response and of damaging/losing the allograft[41]. Conversion to SRL allows on one hand preventing this increased immunological risk when taking into account conversion study results and, at least in theory (and in practice for some types of tumors as discussed in the foregoing), negatively acting on the growth of the neoplasia both on the primary tumor and on the metastatic development.

Another aspect to be considered with respect to malignant neoplasias would be that of patients who experienced a suitably treated neoplasia before the

transplant. It is currently accepted that a transplant can be attempted when after a period of two to five years after diagnosis there is no data suggesting tumor recurrence, except in low aggressive tumors , such as cutaneous tumors that are completely removed and *in situ* (bladder or cervix) tumors[56]. An immunosuppression regimen based on SRL *de novo* could be particularly suitable in these patients for the purpose of reducing the theoretical risk of recurrence if tumor cells persisted in the patient. On the other hand, the use of SRL could, also theoretically since there are no studies regarding this aspect, reduce the time safety margin accepted nowadays.

Severe High Blood Pressure

CNI withdrawal studies in patients receiving SRL almost systematically show decreased blood pressure figures, both diastolic and systolic, and a decrease in antihypertensive drug requirements. In fact, the first publication of the results of trial 310 (early withdrawal of cyclosporine 3 months after the transplant) clearly showed this effect a few weeks after withdrawing CsA in the study group[57], and similar results were observed in other studies[58]. In this sense, a recent joint analysis of several published clinical trials with over 1000 patients in whom CNI is withdrawn shows a significant reduction of blood pressure figures together with renal function improvement[59]. Although there are no studies specifically designed for this purpose, conversion to SRL in patients with a poor controlled blood pressure or who require a large number of antihypertensive drugs may be a suitable strategy for trying to solve or improve this problem.

Post-transplant Diabetes

Post-transplant diabetes (PTDM) is a recognized complication of the calcineurin inhibitors and steroids used in renal transplant, and it is somewhat more frequent in patients receiving TCR. Conversion to SRL accompanied with withdrawal of the calcineurin inhibitor (especially TCR), associated to the prior or subsequent withdrawal of steroids, seems to be a reasonable option in patients who develop glucose intolerance or diabetes after the transplant, in which the relation to immunosuppression drugs seems clear. There are a series of convert patients with good results. Egidi converted 19 patients with glucose intolerance after the transplant and achieved resolution thereof in 11 patients (58%)[7]. A study has recently been published in which an increased insulin resistance and decreased beta cell response are observed after conversion to SRL, which is the opposite of the clinical results described in the foregoing, forcing certain precaution in this matter[60]. However, another study that compares SRL versus MMF in recipients of kidney and pancreas treated with tacrolimus, found similar results in terms of response to an intravenous glucose load, but with lower insulin levels in SRL group. Thus, a higher sensitivity to insulin, and therefore a beneficial effect of SRL would be suggested. More studies are warranted to clarify this issue[61].

Hemolytic Uremic Syndrome

The occurrence of thrombotic microangiopathy is a well recognized complication associated with the use of calcineurin inhibitors[62,63] and when it occurs, modification of the immunosuppression therapy is generally required for the purpose of drastically reducing the CNI dose or, if possible, completely eliminating it. In this sense there are several works showing a positive response for the hematological and renal parameters after conversion to SRL. The Franco series includes experience in Spain with ten renal transplant patients who developed HUS and were converted to SRL. A fast improvement in renal function was shown in 8 out of the ten patients, with an 80% graft survival rate after one year[64]. The Egidi series includes 7 renal transplant patients and 5 kidney and pancreas transplant patients who develop HUS, and improved renal function was observed in all of them after converting to SRL[7]. Other works show similar experiences, including a case in reno-pancreatic transplant[65-67]. There are published works, especially at the end of the 1990s, showing good results for the conversion from CsA to TCR in some cases and from CNI to mycophenolate mofetil in others, but these two strategies do not seem to be very appropriate today. The first conversion is not appropriate because TCR shows a similar risk of developing HUS as does CsA[62], and the second case is not appropriate because conversion to MMF, though feasible, does not seem to be as safe from the immunological point of view as conversion to SRL, which today seems to be the procedure of first choice in handling these patients[68-72]. Conversion to MMF could be reserved for those patients in whom the use of SRL was not appropriate.

Another issue to consider is the situation of patients with HUS/TMA as the underlying cause of end-stage renal disease and those patients who lost their first graft due to HUS/MTA (most cases secondary to CNI). In both cases, it is recommended nowadays to use a CNI-free immunosuppressive regimen to avoid further endothelial damage in genetically predisposed patients. Recently, Oyen has published his experience with 15 patients grafted with SRL without CNI with good results and without observing relapses[73]. Thus, this is a reasonable approach to consider in this type of patients.

An isolated case of a patient developing HUS in patients receiving SRL, especially in patients receiving a graft from marginal donors, has recently been published[74,75].This effect was related to inhibition of endothelial damage repair by the drug prior to the transplant (occurring in the donor)[75] possibly due to blockage of VEGF production[76]. On the other hand, there are several works that seem to demonstrate that the association of SRL and CNI is accompanied by an increase in the incidence of HUS (with respect to the incidence in patients receiving CNI), probably because the first one enhances the toxic effect of CNI on the endothelium[77-80]. Nevertheless, the most correct attitude to take today in patients who develop HUS in the presence of CNI seems to be the conversion to SRL associated to the usual procedures for handling this, as the administration of fresh frozen plasma and/or plasmapheresis.

CONVERSION PROCEDURE

Slow Conversion

The slow conversion consists of the slow reduction of the calcineurin inhibitor after introducing rapamycin for its final discontinuation in a period of 1 to 3 months. SRL loading doses are not normally used and doses of 2-4 mg/d are normally used to start. The CNI dose is reduced by about 25% in each visit (spaced out between 1 and 3 weeks), such that it is completely withdrawn at around the 4th visit after starting with SRL. Conversion to SRL during the initial post-marketing stages was done in this way in most centers with the aim that the slow reduction of CNI would minimize the risk of acute rejection. Experience has shown that the immunosuppression excess maintained during this period is responsible for an excessively high complication rate (especially infections), so it is not recommended today. It is necessary to take into account that the known pharmacokinetic interaction between CsA and SRL means that by gradually reducing CsA doses, SRL levels tend to be reduced so it is necessary to anticipate this and gradually increase the SRL dose (this does not occur in the case of TCR). This together with the repeated visits, which are required during the process, makes it a complicated procedure that has been all but abandoned today after the safety of faster procedures has been demonstrated.

Fast Conversion

In this procedure, the two drugs are overlapped for a shorter period, between one and two weeks, generally reducing CNI by 50% starting from the day that SRL is introduced. The objective of this approach would be to maintain CNI until being certain that SRL levels are sufficient. The first level is usually measured between 5 and 7 days after initiating SRL, and if it is within or close to the target range, CNI is then discontinued. If the level is still low, the SRL dose is increased and CNI is maintained until measuring a second level a week later. It is as safe as the slow conversion from the immunological point of view but it is simpler and has fewer side effects since the risk of overimmunosuppression is minimized.

Sudden Conversion

In this procedure, suitable SRL levels are not awaited. Rather, it is assumed that a sufficient level will be reached in a few days by administering one or two loading doses, such that CNI is suspended the same day that SRL is started, i.e. they are not associated at any time. This procedure has also proven itself to be sufficiently safe from the immunological point of view, and the adverse effects resulting from overlapping the two immunosuppressants is prevented, although higher initial doses are probably required to assure suitable levels from the start and perhaps this, along with the loading dose, can be related to some adverse effects. This procedure was used in trial 316 in which over 500 patients were converted.

Most centers today tend to choose sudden or fast conversions. In this sense, Bumbea et al. describe an initial semi-slow conversion phase (the first 21 patients), then going on to a sudden conversion (the remaining 22 patients)[5].

Other Measures

Some centers have used induction with interleukin-2 monoclonal antireceptor antibodies (anti-IL2r) at the time of conversion in order to reduce the (theoretical) risk of acute rejection to a minimum, showing good results. This is the case of Egidi's work in which daclizumab is used in 6 pancreas-kidney transplant recipients and in two pancreas transplant recipients (alone or combined with kidney transplant)[7]. The Sundberg series shows 21 patients converted abruptly with the concomitant administration of daclizumab, which also shows good results (no acute rejection episode)[81]. However, the use of this practice seems to be questionable today given the low risk of AR described in most conversion series.

WHAT LEVEL RANGE SHOULD BE SOUGHT?

It is important in this sense to take two fundamental aspects into account: 1) the time of the conversion, and 2) the associated immunosuppression. In patients converted after the first year after the transplant and who also receive MMF, a range of levels between 4 and 8 ng/mL (ELISA) seems reasonable, and levels between 6 and 10 ng/ml seem reasonable in those patients who do not receive MMF. When the conversion is done during the first year after the transplant, levels of 10-15 ng/mL must be sought if the patient does not take MMF and between 8 and 12 ng/mL if the patient takes MMF. Levels exceeding 15 ng/mL should rarely be the target today except in very select patients.

HANDLING ASSOCIATED IMMUNOSUPPRESSION

In patients receiving 2 g/day of MMF doses (usually with CsA), the dose should at most be reduced to 1 or 1.5 g/day. CsA interferes with MMF and reduces the levels thereof, but this does not occur with SRL, so after withdrawing CsA, it is to be expected that lower doses allow maintaining similar levels (82). It is also necessary to take into account the common toxicity profile of SRL and MMF, especially on the hematopoietic system, so it is especially advisable to avoid high levels of both. Moderate doses of SRL and MMF constitute a suitable and well tolerated combination in many patients, combining a potent immunosuppressant effect with the antiproliferative effect of both drugs, which could allow, in the authors' experience, safely suspending steroids in a considerable number of patients (although there are no suitable trials that explore this aspect).

The re-introduction of steroids in patients not using them at the time of assessing conversion does not seem necessary. However it does seem reasonable to stop the steroid dose reduction in patients who are following a steroid withdrawal regimen when conversion is considered, and maintaining a minimum of 5 mg of prednisone a day during the first three months after conversion does seem reasonable. If renal function subsequently remains stable it does seem reasonable to continue with the reduction as foreseen.

A special case could be patients who are in *monotherapy* with CsA (without steroids) who, after conversion, are in monotherapy with SRL. There is not much experience in this respect; if the patient shows stable renal function (for example in conversion due to neoplasia) or a progressive renal function impairment and acute rejection is discarded by performing a biopsy, the conversion seems safe enough according to the authors' experiences (data not published), maintaining levels in the high end of the range described in the foregoing, although a second immunosuppressant can also be associated such that it allows maintaining lower levels of SRL. Diekmann reviews the experience of a center on the evolution of 19 patients kept in monotherapy with SRL showing good results[83].

ARE THERE PATIENTS WHO SHOULD NOT BE CONVERTED?

This issue is becoming increasingly important. Despite that most of the published series report benefits in terms of renal function improvement after conversion in a significant percentage of patients[8,10,29], this benefit is not universal and in some patients the elimination of CNI may even cause hemodynamic changes having a harmful effect on proteinuria and on graft function, especially in those patients with a very deteriorated function at the time of conversion. It is therefore accepted today that in patients with a creatinine level above 3 mg/dL other therapeutic options should be considered, and in any case the CNI should not be completely suspended. Something similar occurs with baseline proteinuria, which should contraindicate conversion when it is above 1 or 1.5 g/day. However these figures are orientative and each patient should be assessed in-

Table I. Recommendations summary

Definition	Introducing SRL in a stable patient (3 months after the transplant), completely withdrawing CNI in the following weeks.
Indications	
Chronic Allograft Nephropathy	Do not convert in patients with an already significant renal failure (Cr exceeding 2.5 mg/dL) and/or moderate proteinuria. It is advisable to identify those patients who begin progressive renal function impairment and to consider a graft biopsy early on in order to conduct early conversions before irreversible lesions spread.
Malignant Neoplasias	Usual handling by only decreasing immunosuppression increases the risk of acute rejection. Conversion allows preventing this problem in the first place. In Kaposi's sarcoma its benefit seems clear in tumor regression. Conversion also seems to be particularly indicated in lymphoid tumors and cutaneous tumors.
Severe High Blood Pressure	Consider this therapeutic option in patients with severe high BP who require several hypotensive drugs.
Post-transplant Diabetes	Although a possible harmful effect of SRL on carbohydrate metabolism has recently been described, conversion to SRL seems to be a reasonable option in patients developing a post-transplant DM that is clearly related to the use of CNI (before or after withdrawing steroids).
Hemolytic Uremic Syndrome	Reasonable option in patients with CNI-induced HUS, though it must be taken into account that HUS may occur in the presence of SRL in some circumstances.
Conversion Procedure	It is very advisable to conduct fast conversions such that CNI is eliminated in one or two weeks maximum. It should not be maintained for more time except in exceptional cases.
Sudden Conversion	SRL loading dose of about 10-12 mg the first day. Sudden suspension of CNI the first day. SRL at doses of 3-4 mg/day from the second day.
Fast Conversion	No loading dose. Initial SRL dose of 3-4 mg/day. 50% of the baseline CNI dose. If the first level after 7 days is in range (or above it), CNI is withdrawn directly. If it is under the range, the SRL dose is increased and CNI can be suspended or maintained for another week until the second level.
Target Levels	
In conversions during the first year	Patients without MMF: levels from 10-15 ng/mL Patients with MMF: levels from 8-12 ng/mL It seems reasonable to introduce MMF in this period in order to be able to maintain lower SRL levels and preventing the risk of toxicity.
In conversions after the first year after the transplant	Patients without MMF: levels from 6-10 ng/mL Patients with MMF: levels from 4-8 ng/mL
Post-conversion Follow-up	First level after 7±2 days after starting SRL Second level after 14±2 days. Third level one month after conversion. After that, levels every 2-3 months.
Particularly monitor in each visit	Hemoglobin and hematocrit, leucocytes and platelets. Total cholesterol, HDL, LDL and triglycerides. Proteinuria, it is advisable to test 24-hour proteinuria or proteinuria/creatinuria ratio.
Associated Immunosuppression	
MMF	Do not exceed 1-1.5 g/day. Adjust if there is toxicity.
Azathioprine	Do not exceed 50-75 mg/day
Steroids	Usual doses. Withdrawal can be considered especially in patients receiving MMF.

dependently in any case according to their characteristics.

Patients with uncontrolled severe hyperlipidemia or with considerable anemia or thrombopenia, and generally those patients with presumed poor tolerance to SRL, must be carefully assessed before conducting the conversion.

RISKS OF CONVERSION

Due to Insufficient Immunosuppression

Most of the series show that conversion is a very safe procedure from the immunological point of view, and the risk of acute rejection is minimal,

even when sudden conversions are conducted. In Diekmann's series of 59 converted patients, only 1 case of mild acute rejection can be found, coinciding with excessively low SRL levels 7 months after the conversion, which responded well to steroid pulses[29]. In Bumbea's series, none of the 43 converted patients exhibited acute rejection[5]. With this data is does not seem necessary to associate anti-IL2r during the conversion process, at least not in renal transplant, except in patients who have a high immunological risk. It is important in any case to assure suitable SRL levels during the initial stages, which requires suitable doses and periodic controls.

Due to Excessive Immunosuppression

This aspect is undoubtedly more important than the previous one. Experience shows that complications of this type occur frequently, especially when slow conversions have been conducted in which SRL and CNI are associated for weeks or even months, so it is especially important to conduct conversions as quickly as possible and to try to maintain SRL levels in the recommended range, adjusting the dose as soon as possible. The most frequent complication in this group is undoubtedly oral ulcers. This issue is developed in detail in another chapter of this monograph.

Others

Proteinuria, which has become one of the most crucial conversion risks in recent years, would particularly be part of this group[84-86]. This issue will also be dealt with more in depth in another article of the monograph.

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