Conversion from calcineurin inhibitors to sirolimus in chronic allograft nephropathy: benefits and risks

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Introduction

Chronic allograft nephropathy (CAN) is the most prevalent cause of late kidney transplant failure characterized by progressive loss of graft function in combination with proteinuria and hypertension [1]. Both immunological and non-immunological factors play a role in the development of CAN, and calcineurin inhibitor (CNI) therapy has been identified to be an important non-immunological cause [2–5]. In this context, Nankivell et al. [5] demonstrated in a protocol biopsy study that at least grade I CAN could be diagnosed in all biopsy specimens 3 years after transplantation, and that histological signs of chronic CNI nephrotoxicity are omnipresent after 10 years.

Sirolimus (SRL) is a new, potent, non-nephrotoxic immunosuppressive agent that possesses antiproliferative properties and exerts anti-tumour activity by various mechanisms [6–8]. In a large multicentre study, elimination of cyclosporine A (CsA) after 3 months from a protocol containing SRL and CsA was proven to be beneficial in terms of better renal function, improved renal histology and graft survival [9,10]. Moreover, a single centre study comparing de novo CsA-based immunosuppression with a de novo SRL-based protocol shows better renal function and less CAN 2 years after transplantation [11]. In light of these first positive results and given the proliferative processes predominant in CAN, conversion from nephrotoxic to a non-nephrotoxic and antiproliferative drug like SRL might be a useful approach for prevention or treatment of CAN. So far, conversion from nephrotoxic to non-nephrotoxic regimens such as combinations of azathioprine (AZA) or mycophenolate mofetil (MMF) with steroids had been associated with a higher relative risk of acute rejection after conversion in some studies [12,13]. Another study of conversion to a regimen based on MMF, however, demonstrated no acute rejection at all [14]. In most of these studies the conversion led to better renal function after relatively short follow-up periods; however, according to a meta-analysis by Kasiske et al. [15] no benefit in terms of relative risk of long-term graft failure was achieved comparing the groups with CsA withdrawal with those of continued use of CsA. Therefore, the potent immunosuppressive, antiproliferative drug SRL, that does not show CNI-like nephrotoxicity, gave hope for a new alternative in treatment or prevention of CAN.

To the authors’ knowledge, no study has been published so far that directly compares the impact of conversion to a SRL-based regimen with that of conversion to a MMF-based protocol. Therefore, in the absence of this data the authors neither intend nor are they able to favour conversion to one CNI-free protocol over the other as a general strategy. They rather intend to describe the conversion to SRL as an additional option.

Conversion from CNI to SRL for deteriorating graft function – the clinical experience

Although in many patients CNI-based treatment has been converted to a SRL-based protocol for various reasons – however mainly for CAN – there are a few published studies or experiences with this topic (Table 1). In a first pilot study Dominguez et al. [16] converted 20 patients – 12 of these with chronic CNI toxicity – from CNI-based to SRL-based therapy leading to a statistically significant improvement of kidney function...
after 6 months (233 ± 34 vs 210 ± 56 μmol/l). CNI was withdrawn progressively over 2–8 weeks in most of the patients. Target trough monitoring was not used initially. However, more than half of the patients had SRL concentrations >15 ng/ml. SRL was withdrawn in four patients due to adverse events. Egidi and co-workers [17] converted 64 transplant patients for various reasons. Serum creatinine improved from 2.8 to 2.3 mg/dl in 6 months in patients with CAN or chronic CNI toxicity. Egidi conducted a rapid conversion

<table>
<thead>
<tr>
<th>Studies</th>
<th>n</th>
<th>Deaths/graft losses</th>
<th>Renal function</th>
<th>Rejections post-conversion</th>
<th>Most common adverse effects</th>
<th>Trough levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominguez, 2000 [16]</td>
<td>20</td>
<td>No deaths or graft losses</td>
<td>233 vs 210 μmol/l after 6 months</td>
<td>0</td>
<td>Pneumonia, Bronchiolitis obliterans</td>
<td>Not measured in all pts, however &gt;15 ng/ml in 7/13 11.1 ng/ml after 6 months</td>
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<tr>
<td>Egidi, 2003 [17]</td>
<td>64</td>
<td>2 deaths due to MOF in early post-transplant period/1 graft loss after steroid-resistant AR</td>
<td>2.8 vs 2.3 mg/dl after 6 months in the patients with nephrotoxicity and/or CAN</td>
<td>2/64</td>
<td>Dyslipidemia, transient drop of platelets and white blood count</td>
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<tr>
<td>Morelon, 2003 [18]</td>
<td>50</td>
<td>Responders (32/50) 219 μmol/l vs 160 μmol/l at last follow-up</td>
<td>2.8 vs 2.3 mg/dl after 6 months in the patients with nephrotoxicity and/or CAN</td>
<td>2/64</td>
<td>Hyperlipidemia, anaemia, development of proteinuria 32/50, nephrotic proteinuria 18/50</td>
<td></td>
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<tr>
<td>Dickmann, 2004 [24]</td>
<td>59</td>
<td>Responders (32/59) 2.75 vs 2.2 mg/dl Non-resp. (27/59) 3.15 vs 4.4 mg/dl after 1 year</td>
<td>Responders (32/59) 2.75 vs 2.2 mg/dl Non-resp. (27/59) 3.15 vs 4.4 mg/dl after 1 year</td>
<td>1/59</td>
<td>Anaemia, dyslipidemia, proteinuria</td>
<td>10.7 ng/ml after 1 year</td>
</tr>
<tr>
<td>Renders, 2004 [20]</td>
<td>13</td>
<td>Responders (32/50) 2.38 vs 2.1 mg/dl at last follow-up; ( P = 0.29 ) (analysing the 11 pts. who completed the follow-up)</td>
<td>Responders (32/50) 2.38 vs 2.1 mg/dl at last follow-up; ( P = 0.29 ) (analysing the 11 pts. who completed the follow-up)</td>
<td>1/13 (borderline)</td>
<td>Anaemia, dyslipidemia, urinary tract infection</td>
<td>5.5 ng/ml at last follow-up</td>
</tr>
<tr>
<td>Weber, 2005 [21]</td>
<td>36</td>
<td>Conversion successful in 22 pts. (decrease of creatinine by 25% after 1 year in successful patients)</td>
<td>Conversion successful in 22 pts. (decrease of creatinine by 25% after 1 year in successful patients)</td>
<td>0/13</td>
<td>Anaemia, dyslipidemia</td>
<td>Target 8–12 ng/ml</td>
</tr>
<tr>
<td>Wu, 2005 [22]</td>
<td>16</td>
<td>Conversion successful in 10/16 patients; creatinine in successful patients: 2.91 vs 2.11 mg/dl after 6 months</td>
<td>Conversion successful in 10/16 patients; creatinine in successful patients: 2.91 vs 2.11 mg/dl after 6 months</td>
<td>0/16</td>
<td>Bacterial pneumonia, diarrhoea, skin rash, edema</td>
<td>Mean SRL trough level 3.7 ng/ml</td>
</tr>
<tr>
<td>Bumbea, 2005 [23]</td>
<td>43</td>
<td>2 deaths/1 graft loss 49.4 vs 51.7 ml/min after 2 years</td>
<td>2 deaths/1 graft loss 49.4 vs 51.7 ml/min after 2 years</td>
<td>0/43</td>
<td>Anaemia, hypercholesterolemia, de novo proteinuria &gt;1 g/day in 28%</td>
<td>Target 8–12 ng/ml</td>
</tr>
<tr>
<td>Peddi, 2005 [19]</td>
<td>60</td>
<td>2 deaths (myocardial infarction, malignancy)/3 graft losses 2.0 vs 2.0 mg/dl after 1 year</td>
<td>2 deaths (myocardial infarction, malignancy)/3 graft losses 2.0 vs 2.0 mg/dl after 1 year</td>
<td>2/60</td>
<td>Dyslipidemia, diarrhoea, anaemia, edema, skin rash, pneumonia</td>
<td>10.0 ng/ml after 1 year</td>
</tr>
<tr>
<td>Watson, 2005 [25]</td>
<td>40; 20 CNI continuation, 20 SRL</td>
<td>No deaths/2 graft losses Randomized, controlled study: Comparison after 1 year: SRL vs CNI group; 46 vs 32 ml/min (( P &lt; 0.001 ))</td>
<td>No deaths/2 graft losses Randomized, controlled study: Comparison after 1 year: SRL vs CNI group; 46 vs 32 ml/min (( P &lt; 0.001 ))</td>
<td>0/40</td>
<td>Rashes</td>
<td>5–15 ng/ml</td>
</tr>
</tbody>
</table>

MOF: multi-organ failure.
with abrupt stop of CNI therapy and one loading dose of SRL. Morelon and Kreis [18] report their Necker Hospital experience of conversion of 50 patients, 48 of them with CAN. They observed an improvement of kidney function in 32 out of 50 patients. However, later during the follow-up period these patients showed decrease of renal function, but renal function was still better at the end of the follow-up period than at conversion in the responders (218 vs 160 μmol/l) [18]. They also observed new onset of proteinuria in 32 out of 50 patients, even nephrotic range proteinuria in 18 of them. Six of these 18 patients responded to angiotensin converting enzyme inhibitor (ACE-I) treatment. Peddi and co-workers [19] conducted a conversion study in 60 patients with moderate renal insufficiency. Creatinine clearance remained stable (51 vs 53 ml/min). Renders and co-workers demonstrated an improvement of renal function in 10 of 13 patients on combination therapy of SRL and MMF. Interestingly, Renders et al. [20] found higher SRL and MMF trough levels as expected for the low administered doses of both drugs, suggesting an interaction of SRL and MMF leading to increased levels of both drugs. Weber et al. [21] converted 36 patients with CNI toxicity or CAN and demonstrated an improvement of renal function in 22 patients. They differentiated between patients with CNI nephrotoxicity and CAN with or without signs of chronic rejection and found that the groups with nephrotoxicity and CAN without signs of chronic rejection benefited more from conversion, whereas the patients with CAN and signs of chronic rejection had a poorer outcome. Wu and colleagues [22] converted 16 patients, 10 of these with improvement of kidney function after 6 months with low SRL trough levels of 3.7 ng/ml in combination with MMF and steroids. Bumbea and colleagues [23] converted 43 patients and were able to demonstrate an overall stabilization of kidney function after 2 years. However, they encountered de novo proteinuria > 1 g/day in almost one third of the patients, five of these with nephrotic range proteinuria. They found the absence of proteinuria and the application of antihypertensive therapy at time of conversion were predictive factors for a successful conversion [23]. In our own experience in patients with chronic allograft dysfunction (CAD), as reported in 2004, we encountered improvement of renal function in 54% of patients, whereas the remaining patients suffered from further deterioration of graft function after 1 year [24]. Watson and co-workers [25] published the only controlled, randomized conversion study comparing 20 patients who were converted to SRL with 20 patients who were left on conventional CNI therapy. They encountered a significant improvement of glomerular filtration rate (GFR) in the SRL group after 3 months and 1 year, whereas GFR deteriorated in the CNI group. In this trial, conversion was not associated with an increase of proteinuria. The most common adverse events of all these studies were dyslipidemia, anaemia, infectious and non-infectious pulmonary problems, mouth ulcers, skin rash and diarrhoea [16–25]. At the end of the follow-up, which ranged from 6 months to over 2 years, 58–94% of patients still received SRL reflecting a wide range of dropout rates. Hyperlipidemia in SRL treatment is mostly dose-dependent, and most investigators found non-infectious pulmonary adverse events in patients with trough levels >15 ng/ml. These effects appear to be reversible with dose reduction or withdrawal of the drug [16–25,33]. Furthermore, increase of urinary protein excretion in patients who already showed proteinuria at conversion appeared as a major problem in some of them. Acute rejection rate ranged between 0 and 4%. Concluding from these studies and also in our experience, problems during the conversion – except for proteinuria – are more likely to arise from over-immunosuppression or from drug-related toxicity than from under-immunosuppression. A short CNI–SRL overlap phase seems to be advantageous in terms of avoiding over-immunosuppression, although some investigators also reported overlap phases of 1 month or longer without major problems. In addition, most of the above mentioned side effects appear to be manageable by either dose reduction or treatment with lipid-lowering agents, ACE-I or angiotensin receptor blockers (ARB) and erythropoetin or its derivatives.

Conversion from CNI to SRL for CAN – who will benefit?

According to the above studies, between 20 and 46% of patients with allograft dysfunction do not respond to conversion from CNI to SRL. In a study to identify predictors of a favourable response, the number of rejections prior to conversion, proteinuria, a higher chronic Banff score and a higher score of vascular intimal thickening were associated with non-responder status in a univariate analysis [24]. In a multivariate analysis, only proteinuria was the predictive parameter. Proteinuria below 800 mg/day had a positive predictive value of 90%. This is in accordance with a study of CsA withdrawal resulting in a MMF-based regimen by Ducloux and co-workers [26] describing a strong correlation between baseline proteinuria and improvement of renal function. In this context, proteinuria can be seen as a surrogate marker for advanced structural damage of the kidney. Responders in our study had a tendency towards lower creatinine values at conversion (2.75 ± 0.75 vs 3.15 ± 1.02 mg/dl; \( P = \text{n.s.} \)); however, this did not reach statistical significance. Egidi (personal communication) found a significant difference in serum creatinine between responders and non-responders (2.7 ± 0.9 vs 3.7 ± 1.7 mg/dl). Recently, an amendment to a large international controlled, randomized conversion study excluded patients with creatinine clearance <40 ml/min from recruitment due to disappointing results in terms of renal function and safety [27]. In another study, we demonstrated that conversion in patients with CAD not only led to an increase of proteinuria, but also to a loss of renal functional reserve and
increased intraglomerular pressure, which supports the hypothesis that haemodynamic changes play a significant pathophysiological role and that hyperfiltration in kidneys with established structural damage leads to increased proteinuria [28]. Therefore, an early conversion is warranted to prevent the progression of CAN and to avoid hyperfiltration and proteinuria. However, SRL has also been associated with a reversible deterioration of kidney function and an increase of proteinuria in glomerulonephritis of native kidneys and in certain models of experimental glomerulonephritis, suggesting that haemodynamic changes might not be the only explanation for the increase in proteinuria and that in some patients with pre-existing glomerular damage, proteinuria might be directly mediated by SRL [29,30]. We propose conversion for CAN at creatinine values below 2.5 mg/dl and proteinuria below 800 mg/day. In patients with higher proteinuria, extreme caution should be employed when considering conversion. In overt proteinuria, conversion to SRL could even be considered contra-indicated.

Since there are implications that glomerular haemodynamic changes may contribute to post-conversional proteinuria [28], treatment with ACE-I or ARB should be attempted before conversion. In our experience this is a successful strategy.

So far there are no long-term results of conversion beyond 2 years. In order to clinically prove the possible long-term benefits of conversion to SRL in terms of reduced progression of CAN or even of reduced cardiovascular morbidity, randomized, controlled studies with a long-term follow-up are necessary comparing the conversion to SRL with a protocol containing CNI at a reduced dose or discontinuation of CNI. Weir and colleagues [31] suggested the latter two possibilities after conducting a controlled randomized trial of conversion to MMF for CAN.

No study has been published so far comparing the benefit of conversion from a CNI-based to an MMF-based vs SRL-based regimen. Risk factors for bad outcome, proteinuria have been identified for conversion to MMF by Ducloux et al. [26] and for conversion to SRL by Bumbea et al. [23] and Diekmann et al. [24]. Bumbea also identified a correlation with the LDH and the existence of antihypertensive medication at conversion. Furthermore, Dudley and the MMF Creeping Creatinine Study Group [14], as well as most investigators who have published studies on conversion to SRL for CAN, suggest that early conversion might be more beneficial – partly based on histological findings in pre-conversion allograft biopsies – however, there are no published studies proving the benefit of early vs late conversion.

**How to convert from CNI to SRL? – how to avoid the pitfalls?**

Generally conversion for prevention or treatment of CAN will be done in a chronic situation. Instead of acute rejection, the most important adverse events result from overdosing of SRL or overimmunosuppression [16,20,32]. Anglocheau and colleagues [33] were able to show that patients carrying the CYP3A4-1B or the CYP3A5-1 alleles required significantly more SRL to achieve adequate blood trough concentrations. Therefore, in the future a pharmacogenetic approach assessing CYP3A4 and CYP3A5 might be helpful in order to better manage SRL dosage at the beginning of the conversion process.

Conversion should be individualized according to the clinical situation of each patient, i.e. time after transplantation, concomitant immunosuppression, individual immunological risk, specific problem leading to conversion and other clinical events. For example, an African-American patient with obesity, post-transplant diabetes and hypertension less than 1 year after transplantation is likely to be in a different clinical situation and to have a different immunological risk than a Caucasian patient 10 years after transplantation weighing less than 50 kg.

A long overlap of SRL and CNI should be avoided. We propose a short overlap phase of 7–10 days and moderate target trough levels of 8–12 ng/ml (Figure 1). A short turn-around time for determination of trough concentrations is essential for the management of the drug during conversion. We propose starting with 3–4 mg of SRL daily without a loading dose. On day one, the CNI should be reduced by 50%. Due to metabolic interactions, SRL should be given 4 h after CsA, whereas SRL and tacrolimus can be given simultaneously. After achieving the SRL target trough concentration after 7–10 days, CNI treatment should be stopped. Steroid treatment should not be changed during the conversion. A maximum MMF dose of 1.5 g/day is recommended, although the combination of SRL and higher MMF doses facilitates manifestations of myelosuppression such
as anaemia. Myelosuppression and gastrointestinal side effects may lead to a dose reduction of MMF. Always taking into account the patient’s individual situation, other conversion schemes are possible. At the University of Memphis, Tennessee, abrupt cessation of CNI with a single loading dose of SRL of 10 mg followed by 5 mg/day in African-Americans or a loading dose of 8 mg followed by 4 mg/day in Caucasians is successfully practiced [17]. The proposed schemes and doses can only be rough estimates and need to be adjusted to each individual patient’s clinical situation. Decrease of haemoglobin after conversion to SRL, especially in conjunction with impaired graft function, can be a problem. Especially in this case, the lowest possible SRL dose should be administered. In most of the cases anaemia reacts to treatment with erythropoetin or a derivative. If anaemia is a problem in combination with another myelosuppressive therapy, e.g. MMF, then dose reduction of the concomitant immunosuppressive medication should be performed first. The need for complete SRL withdrawal because of anaemia is a rare event. Increase in lipid levels can occur and SRL is dose-dependent. Close monitoring and statin treatment for hyperlipidemia is recommended. Two distinctive kinds of pulmonary adverse events have been reported: pulmonary infections that respond to antibiotic treatment and interstitial pneumonitis in the absence of an infectious agent, which is characterized by lymphocytic alveolitis and is generally completely reversible after dose reduction or complete withdrawal of SRL [34]. In some cases, unexplained epistaxis after introduction of SRL – not leading to any intervention – has been reported [24]. Mouth ulcers occur in some conversion patients and seem to reflect over-immunosuppression. Antiseptic mouth rinse is helpful and usually mouth ulcers improve after lowering the immunosuppressive load and after some time after conversion. However, in some patients this problem can be severe and can lead to withdrawal of the drug [32]. According to Mahé and colleagues [35], skin problems also occur frequently in conversion patients and – although mostly of a mild nature – often lead to patient discomfort to an extent that requires drug discontinuation. Table 2 summarizes general recommendations for conversion.

**Conclusion**

Conversion to SRL for CAN is safe and can lead to better renal graft function if performed early enough, before chronic structural damage is too far advanced. First studies identified renal functional parameters such as creatinine and 24-h-proteinuria as helpful tools for a therapeutic decision. However, there appears to be a ‘point of no return’, after which conversion to SRL will not result in preservation of renal function for a longer time than achieved under CNI treatment, i.e. little is to be expected if conversion is performed in patients with already advanced CAN. In addition, in some patients with post-transplant glomerular disorder, SRL might have a detrimental effect, as observed by Morelon and colleagues [18] and by Dittrich and co-workers [36]. Therefore, the use of SRL

<table>
<thead>
<tr>
<th>Table 2. General recommendations for conversion from CNI-based to SRL-based immunosuppression for CAN</th>
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<tbody>
<tr>
<td><strong>Individualize conversion to SRL</strong></td>
</tr>
<tr>
<td>Thoroughly discuss possible benefits and adverse events with the patient</td>
</tr>
<tr>
<td>Consider transplant biopsy before conversion</td>
</tr>
<tr>
<td>Rapid decrease of CNI</td>
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<tr>
<td>Initial SRL dose 3-4 mg/day</td>
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<tr>
<td>Careful drug monitoring</td>
</tr>
<tr>
<td>Adjust MMF dose in patients who were previously treated with CsA</td>
</tr>
<tr>
<td>Consider possible metabolic interactions</td>
</tr>
<tr>
<td>Leave steroid dose unchanged during conversion process</td>
</tr>
<tr>
<td>Monitor and control lipids</td>
</tr>
<tr>
<td>Monitor and control proteinuria</td>
</tr>
<tr>
<td>Convert early</td>
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</tbody>
</table>

ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; CNI: calcineurin inhibitors; CsA: Cyclosporine A; MMF: mycophenolate mofetil.

Please note: These are general recommendations. Doses recommended in this table might have to be adjusted to the patient’s individual situation, i.e. body weight, ethnicity, immunological risk, concomitant treatment, comorbidity.
in these patients should be handled with extreme caution. The exact definition of the best time for conversion is still a field of research for future controlled studies (e.g. conventional histology, genomic analysis of biopsies, proteomics). However, clinical experience suggests that the benefit will be greater in early conversion. Since there are strong implications that structural damage happens before deterioration of creatinine in CAN [5], future studies will also have to demonstrate if switch before the first symptoms of CAN – e.g. systematic conversion a certain time after transplantation – as a preventive measure rather than a switch as a treatment strategy for established CAN with deterioration of kidney function, is even more beneficial.

This article focuses on conversion from CNI-based to SRL-based immunosuppression for CAN; however, the proposed conversion methods can also be applied to other indications, such as post-transplant malignancy or neurotoxicity.

Conflict of interest statement. The authors state to have no conflict of interest.

(See related article by Bumbea et al. NDT 20: 2517–2523)

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Bone morphogenic protein-7 and the kidney: current concepts and open questions

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Keywords: Bone Morphogenic Protein-7 (BMP-7); Fibrosis; Epithelial Mesenchymal Transition (EMT); Chronic Kidney Disease (CKD); Chronic Renal Failure (CRF)

Introduction

Several recent studies have demonstrated unequivocally that administration of bone morphogenic protein-7 (BMP-7) has a therapeutic effect in various animal models of acute and chronic renal injury (Table 1). However, the underlying mechanisms of BMP-7 action in the kidney remained largely unknown in these initial reports. Here, novel aspects regarding the biology of BMP-7 in the kidney will be discussed.

What is BMP-7?

BMP-7, also known as Osteogenic protein-1 (OP-1), is one of 15 currently known BMPs, which are structurally and functionally related and which are part of the transforming growth factor β (TGF-β) superfamily of growth factors [1]. BMP-7 was originally identified as a regulator of cartilage and bone formation [2]. However, BMPs have also been shown to regulate the growth, differentiation, chemotaxis and apoptosis of various cell types, including epithelial, mesenchymal, haematopoietic and neuronal cells [3]. BMPs are highly conserved across animal species and mature human and mouse BMP-7 share 98% amino acid sequence identity [4]. BMP-7 is synthesized as a large precursor protein and the mature, biologically active BMP-7 is generated by proteolytic removal of the signal peptide and pro-peptide [5]. The mature BMP-7 is a glycosylated...