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# Conversion of Calcineurin Inhibitors With Mammalian Target of Rapamycin Inhibitors After Kidney Transplant

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## Abstract

**One way to overcome chronic allograft nephropathy induced by calcineurin inhibitors in immunosuppression protocols for organ transplants is to replace such inhibitors with mammalian target of rapamycin inhibitors, which are not clinically nephrotoxic because they have better renal function. If patients tolerate replacement, there could be a clear preference for mammalian target of rapamycin inhibitors as a maintenance immunosuppressant after renal transplant. This replacement could be sufficient if it were used for a certain time after calcineurin inhibitors. This review considers the conversion effects of calcineurin inhibitors with mammalian target of rapamycin inhibitors from the view point of kidney function during different periods after a kidney transplant.**

## Introduction

Current routine maintenance protocol for most HLA-mismatched kidney recipients is composed of calcineurin inhibitors (CNIs), an antiproliferative agent, and steroids.<sup>1,2</sup> This protocol has been able to improve the 1-year survival of kidney transplants in most centers, and decrease rates of acute rejection (AR).<sup>1,3</sup> However, it does not solve the problem of chronic rejection<sup>1,4</sup> and does not provide proper renal function.<sup>3,5</sup> During chronic rejection, CNIs lead to interstitial fibrosis/tubular atrophy, which lead to

nephrotoxicity and subsequent chronic allograft nephropathy (CAN).<sup>6-9</sup> The disadvantages of CNIs in this protocol are not restricted to renal transplant and can be seen in other solid-organ transplants.<sup>10</sup> One way to decrease such destructive effects of CNIs is to replace them with mammalian target of rapamycin (mTOR) inhibitors such as sirolimus,<sup>3,4,8,9,11,12</sup> which are immunosuppressants,<sup>4,9,10</sup> but relatively nonnephrotoxic ones.<sup>4,9,10,12,13</sup> Compared with CNIs, mTORs cause better renal function and lower tissue chronicity in kidneys and other organ transplants.<sup>3,7,11,14,15,16</sup> The significance of such replacement is important when considering the fact that blood levels of CNIs cannot predict their own nephrotoxic effects. This is because they have different liver metabolism and intestinal absorption in different people.<sup>10</sup> But because some mTORs lead to adverse effects (eg, wound healing delay and increased rate of biopsy-proven AR),<sup>3,4,16</sup> the immediate posttransplant replacement of CNIs with mTORs would be unpleasant; such replacement is better if it is used after 3 to 6 months.<sup>3,4,7,17</sup> Firstly, such strategy prevents CNI-induced nephrotoxicity and CAN in different organ transplants<sup>9,18</sup>; secondly, it allows CNIs primary protection from AR<sup>4,5</sup>; third, it prevents the adverse effects of mTOR inhibitors (eg, wound healing delay<sup>4,5</sup>); and finally, it increases the number and effects of T-regulatory cells in prevention of the AR processes.<sup>5,19,20,21</sup>

Several trials have been tried to define the exact effects of such conversion. Some of them have left us in doubt of replacement,<sup>5</sup> and other studies have sought to help in eradicating such doubt and have been conducted to consider the conversion effects of CNIs with mTOR inhibitors from the view point of kidney function and the patient's outcome during different periods after the kidney transplant.

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### Major strategies for sirolimus therapy in clinical organ transplant

Two strategies are used for sirolimus therapy in clinical organ transplant. The first strategy includes de novo use of sirolimus in combination with either mycophenolate mofetil or reduced amounts of CNIs (ie, cyclosporine or tacrolimus), and the second one uses conversion from a CNI-based regimen to sirolimus either preemptively during 12 to 24 weeks<sup>4,18</sup> or after the well-recognized adverse effects of CNI maintenance therapy (ie, impaired renal function or CAN).<sup>9,18</sup> The second strategy is a better option because it avoids the CNI-associated risks of nephrotoxicity and CAN while allowing for early protection from AR afforded by mTOR inhibitors.<sup>5,22</sup> Also, reintroduction of CNIs would be safe in patients withdrawn from sirolimus for their adverse effects.<sup>23</sup>

After FDA-approval of sirolimus in combination with cyclosporine and steroids in kidney transplant in 1999,<sup>4</sup> sirolimus was evaluated in cyclosporine-sparing protocols. Based on our search, in the first clinical trial using mycophenolate mofetil and steroids, 78 kidney transplanted patients were randomized to receive de novo sirolimus or cyclosporine. The results showed similar graft and patient survivals as well as biopsy-proven AR, but better renal function with a higher calculated glomerular filtration rate at both one-<sup>24</sup> and two-year analyses<sup>25</sup> in the sirolimus group compared to the cyclosporine group. After that trial, many prospective trials demonstrated a similar positive effect of conversion on renal function at different times after transplant. In these trials, patients receiving maintenance therapy with mycophenolate mofetil, steroids, and cyclosporine continued to receive cyclosporine or to be converted to sirolimus. Cyclosporine avoidance at different posttransplant times ranging from 10 to 24 days in the SMART study,<sup>3</sup> to 3 months in the CONCEPT study,<sup>26</sup> to 6 months in the SPIESSER trial,<sup>27</sup> and to 8 years<sup>28</sup> showed similar patient survival, graft survival, and biopsy-proven AR rates in both cyclosporine- and sirolimus-treated patients. However, all these studies showed significantly better renal function in mean serum Cr levels and/or glomerular filtration rate at month six,<sup>1</sup> the first year,<sup>1,3,16,28,29</sup> the second year,<sup>23,30,31</sup> the third year,<sup>31</sup> the fourth year,<sup>32</sup> and the fifth year<sup>27,33</sup> after transplant in sirolimus-treated patients compared to cyclosporine-treated patients.

Among the above trials, are there 2 large prospective ones: CONVERT<sup>29</sup> and Spare-the-Nephron<sup>30</sup> on 830 and 305 transplants. The 2-year-outcome results showed that maintenance immunosuppression with a mycophenolate mofetil-based regimen in combination with steroids provides an improvement in renal function in the sirolimus group compared with a CNI-containing regimen; however, biopsy-proven AR rates remained low, and consistent for each group.

Such effects of sirolimus conversion are not restricted to adult-age ranges and could also be seen in pediatric-age ranges. For example, 2 studies experiencing pediatric renal transplanted patients at the second<sup>8</sup> and the fifth years<sup>34</sup> after conversion from CNIs to sirolimus revealed that such conversion could be well-tolerated and successful with improved renal function and no increased risk of rejection.

### Sirolimus conversion in organ transplant

Different trials have shown that sirolimus conversion can preserve<sup>15,35</sup> or reverse<sup>36,37,38,39</sup> renal function in other organ transplanted patients receiving CNI-based immunosuppression. These studies found sirolimus as a useful alternative immunosuppressant, allowing CNI withdrawal in transplant recipients with renal impairment. Surprisingly, sirolimus also has antineoplastic, antiviral, and antiatherogenic advantages over other immunosuppressive agents.<sup>13,40</sup>

It is important to note that sirolimus conversion at different points in time after renal transplant does not have the same results.<sup>22</sup> It is more likely that conversion at early months could be beneficial to preserve the graft function,<sup>28</sup> improve CAN grading,<sup>25,41</sup> and lower incidence of sirolimus adverse effects.<sup>12</sup> The last benefit suggests that sirolimus toxicity is higher when patients are already weakened by prolonged immunosuppressive treatment. It also has been suggested that sirolimus conversion among patients with better baseline renal function<sup>29</sup> as well as low baseline proteinuria<sup>12,42,43</sup> is associated with excellent and brilliant graft as well as patient survival. But in reverse, improper baseline graft function continues to have progressive deterioration in renal function probably due to the progression of chronic alloantigen-dependent rejection that is not controlled by either CNI or sirolimus.<sup>12,44,45</sup>

Two recommendations would be noted regarding the use of sirolimus: (1) It should be considered the occurrence of acute nephrotoxicity by sirolimus. The reported absence of nephrotoxicity by sirolimus is based on clinical studies investigating the renal effects of sirolimus at therapeutic concentrations (5-15 ng/mL). In fact, it has been reported in the rat, by renal micropuncture, that high doses of sirolimus and its consequent high blood levels can acutely affect renal dynamics determining renal vasoconstriction and thus reduce the glomerular filtration rate, with a glomerular pattern resembling that observed with tacrolimus<sup>46</sup>; and (2) owing to the wide pharmacokinetics variability and the narrow difference between therapeutic and toxic ranges of sirolimus, its therapeutic drug monitoring after kidney transplant has been proposed. A key reason for such measurement is that its dose is a poor predictor of drug exposure. It could be added 2 other reasons: Firstly, impairment of liver function can influence the clearance of sirolimus and secondly, drug interactions might cause an increase or decrease in sirolimus blood concentrations. The latter is because of its metabolism by the cytochrome P450-3A4 isoenzymes.<sup>47</sup>

### Studies that disagree

We found some disagreement in studies in which no better renal function is seen after conversion from tacrolimus, but not cyclosporine (according to our search), to sirolimus in patients receiving mycophenolate mofetil and steroids. For example, in 2 trials, conversion from tacrolimus to sirolimus at the first<sup>6</sup> and the third<sup>17</sup> month after transplant in kidney recipients was poorly tolerated because of statistically significant AR and no difference in graft function at the twelfth and sixth months.

### Combination therapy by cyclosporine and sirolimus

It is not a good idea to use cyclosporine and sirolimus simultaneously.<sup>10,48</sup> Cyclosporine minimization using sirolimus may improve the renal function in short term<sup>49,50</sup> and long term,<sup>51</sup> but its maintained exposure is still progressively nephrotoxic over time.<sup>50</sup> On the other hand, sirolimus can synergize with CNIs,<sup>52,53</sup> increase the nephrotoxicity of cyclosporine,<sup>9,10,12,13,54</sup> and decrease the glomerular filtration rate.<sup>6</sup> In renal allograft recipients, early and complete withdrawal of cyclosporine is more

preferable than continuing this regimen.<sup>31,48,55</sup> Calcineurin inhibitors exacerbate ischemic injury in transplanted kidneys, but sirolimus has no such direct hypoxic effects yet it prevents cyclosporine-induced toxicity in the ischemic kidneys.<sup>52</sup>

### Effects of sirolimus on mycophenolate mofetil

Some studies revealed the advantages of sirolimus and the disadvantages of cyclosporine on mycophenolate mofetil. Low-dose sirolimus therapy in combination with concentration-adjusted mycophenolate mofetil therapy leads to the improvement of organ function late after renal transplant.<sup>45</sup> Cyclosporine, but not sirolimus, inhibits mycophenolic acid enterohepatic recirculation, ultimately resulting in 50% lower mycophenolic acid daily exposure as compared with sirolimus in renal transplants. These findings are important in the case of conversion from cyclosporine to sirolimus to minimize cyclosporine toxicity or maximize the inhibitory effect of mycophenolate mofetil on the immune response.<sup>2</sup>

### Conclusions

The various advantages and disadvantages of cyclosporine and sirolimus lead to the concept of sequential immunosuppression. To date, complete CNI avoidance seems to be inappropriate; thus, many patients receive a CNI during the early postoperative period when AR episodes and wound healing disturbances occur. In a long period, however, the CNI may be replaced by an mTOR inhibitor to reduce nephrotoxicity and the occurrence of de novo malignancy. When tolerated by the patient, there is a notable preference for mTOR inhibitors as a maintenance immunosuppressant after renal transplant<sup>4</sup> even though it is unknown to what extent avoidance of CNIs could improve graft survival.<sup>56</sup>

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