

## Tacrolimus in solid organ transplantation

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Tacrolimus (FK506 or Prograf®) is a macrolidic antibiotic, which acts as a calcineurine inhibitor. Its pivotal mechanism of action is the blocking of calcineurin phosphatase activity and the subsequent production of IL-2 and other cytokine production<sup>1</sup>. It is ten to one hundred

times more potent drug compared to cyclosporine in a weight 1/1 basis<sup>2</sup>. Tacrolimus may also inhibit nitric oxide synthetase activation<sup>3</sup> and enhance apoptosis<sup>4</sup>.

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### Tacrolimus in kidney transplantation

The results of the Multicentric Tacrolimus European Renal Study in a triple drug scheme (tacrolimus with azathioprine and steroids) showed that the acute rejection episodes frequency as well as the frequency of episodes of steroid resistant rejection was significantly lower in the group of patients taking tacrolimus compared with the group of patients taking cyclosporine A. In the same study the group of tacrolimus presented a tendency to lower rate of chronic rejection compared to cyclosporine group (5.2% and 9.3% respectively,  $p=0.185$ , Kaplan Meier method)<sup>5</sup>. Records from the UCLA – UNOS kidney Transplant Registry support that tacrolimus improves significantly the long-term kidney graft survival compared to cyclosporine A. The half – life kidney graft survival, considered as the time from transplantation to the point of 50% loss of kidney grafts, was found to be 14 years with tacrolimus and 8 – 9 years with the cyclosporine A ( $p= 0.04$ )<sup>6</sup>.

The results of five year follow up of the European Study showed that there is no difference in the graft and patient survival, the frequency of chronic rejection in the group of tacrolimus is significantly lower compared to the group of cyclosporine A (6.6% versus 15.3%,  $p<0.01$ ). In the same study the projected kidney graft half – life was 15.8 years and 10.8 years respectively<sup>7</sup>. The American Multicentric Study after a five year follow up concludes that the immunosuppression with tacrolimus presents significantly lower risk of kidney graft loss compared to cyclosporine A, without any raise of complications related to chronic immunosuppression. The frequency of method failure was significantly higher in the group of cyclosporine A<sup>8</sup>.

In a recent multicentric prospective study (50 centers), tacrolimus (287 pts) was compared to microemulsion formulation of cyclosporine (CsA ME – 273 pts). The tacrolimus group presented significantly lower number of acute rejection episodes in a triple drug scheme (azathioprine, steroids) after six month follows

up compared to CsA ME group (19.6% versus 37.3%,  $p=0.0001$ )<sup>9</sup>. In the same study it was noticed significantly lower number of steroid resistant acute rejection episodes. The difference in the acute rejection episodes persisted after the completion of 12 months follows up, as it is shown from another report of the same study group<sup>10</sup>. Recently, a single center's results showed that patients receiving tacrolimus had significantly greater 6-year graft survival (81% versus 60%,  $p=0.049$ ) and a higher projected graft half – life (15 versus 10 years) than those receiving CsA ME<sup>11</sup>. In the same study, morphometric analysis of graft biopsies showed that interstitial fibrosis was significantly greater in the CsA ME group over one year. Until recently it was thought that tacrolimus and cyclosporine express nephrotoxicity which is indistinguishable by histopathologic examination and that TGF –  $\beta 1$  plays a significant role in the acute and chronic toxicity of the two drugs<sup>12</sup>.

A recent meta – analysis comparing tacrolimus with cyclosporine in kidney transplantation confirms the lower risk of acute rejection in the tacrolimus treated patients but at the same time shows a higher frequency of diabetes mellitus in the same group of patients<sup>13</sup>.

Tacrolimus offers better quality of life because cyclosporine has been connected with facial changes, gum hypertrophy and hirsutism<sup>14-16</sup>.

Regarding the resistant acute rejection manipulation in patients taking cyclosporine a, it has been shown that tacrolimus can reverse effectively resistant rejection in the 78% of cases, with low percentage of relapse and acceptable safety profile<sup>17</sup>. Similar results were presented in the study of patients taking the microemulsion formulation of cyclosporine<sup>18</sup>.

Studies concerning the hospital cost during the initial six months after kidney transplantation showed that treatment with tacrolimus costs less compared with the treatment with CsA ME<sup>19,20</sup>.

In pediatric kidney transplantation the tacrolimus use resulted in lower rate of acute rejection episodes<sup>21</sup>

and acceptable safety profile regarding the appearance of lymphoproliferative disorders<sup>22</sup>. Also it can be used as rescue therapy in cases of refractory acute rejection or in cases of CsA toxicity<sup>23</sup>.

Except acute rejection, there are other factors that influence the long-term graft survival. Cardiovascular disease is the leading cause of death of patients with renal transplantation and the use of various immunosuppressive agents must always take into account or consideration the side effects of these agents that cause or aggravate preexisting cardiovascular disease. Hypertension and lipid abnormalities are well known side effects of ciclosporine. The results of a three-year duration American Study showed significantly lower levels of total cholesterol, triglyceride and LDL levels in the patients taking tacrolimus when compared with those taking ciclosporine<sup>24</sup>. Similar results were reported by the European Multicenter Study<sup>25</sup>. The same results were shown when CsA was converted to tacrolimus while there was no change in the Lp(a) and homocysteine levels<sup>26</sup>. The need for antihypertensive agents was lower in the tacrolimus group in the American Study<sup>8</sup>. Lower arterial blood pressure was found in patients taking tacrolimus when compared to patients taking CsA<sup>24,25,27,28</sup>. The conversion from CsA to tacrolimus was followed by significant reduction in blood pressure<sup>29</sup>.

#### **Tacrolimus in simultaneous kidney – pancreas (SKP) transplantation**

It has been reported that tacrolimus is preferable in simultaneous kidney – pancreas transplantation<sup>30</sup>. In a prospective trial, tacrolimus was used with and without induction therapy. Patient and graft survival did not show significant difference between the two groups<sup>31</sup>.

In a recent multicenter study of SKP transplantation with induction therapy, pancreas survival was significantly better at 1 year in the tacrolimus group (91.2% vs 73.9%;  $p < 0.001$ ) compared to the CsA ME group, although there was no difference in patient or kidney graft survival rates. There were, also, significantly fewer biopsy proven rejection episodes of grades 2 and 3 in the tacrolimus group ( $p = 0.0015$ ) and the hospital stay was shorter ( $p = 0.025$ )<sup>32</sup>.

In SKP transplantation with tacrolimus as basal immunosuppression patient survival was  $> 93\%$  at one year and kidney and pancreas graft survival rates were  $> 89\%$  and  $> 81\%$  respectively<sup>32,33</sup>.

#### **Tacrolimus in liver transplantation**

Rejection patterns and rates have traditionally been used as measures of drug efficacy. Results from multicenter randomized studies of liver transplant recipients consistently show lower rates of cellular rejection, steroid resistant rejection and chronic rejection in tacrolimus treated patients than in those who received the old formulation of CsA<sup>34-37</sup>. Moreover, more patients

were switched from CsA to tacrolimus<sup>37-39</sup>. One meta – analysis by Bissuti and Holt supports that tacrolimus is connected with better graft survival after a three year follow up and lower frequency of chronic rejection<sup>40</sup> while the results from extended follow up of the early US and European studies to 5 years and 2 years, respectively, suggested better survival for patients receiving tacrolimus than for those receiving CsA although this difference was not significant<sup>38,39</sup>.

A comparative study between tacrolimus and CsA ME formulation showed that graft and patient survival was similar in both groups in the end of the first three months after liver transplantation. There was no significant difference in the number of acute rejection episodes or steroid resistant rejections between the two groups but the number of patients converted from tacrolimus to ciclosporine was lower compared with the number of patients converted from ciclosporine to tacrolimus. In spite the fact that the safety profile of the two drugs was similar, this study disclosed that hypertension and hyperuricemia were less frequent in patients taking tacrolimus while diarrhea was more frequent in patients under tacrolimus compared with the patients under ciclosporine<sup>41</sup>. A similar study of three month duration and smaller number of patients, showed that the immunosuppressive protocols (tacrolimus vs CsA – ME) were equally effective but it was noticed that in the CsA – ME group it was necessary preemptive treatment with antibodies and that azathioprine was given in 69.6% of cases<sup>42</sup>.

Rabkin and collaborators, in a recent comparative study (open – prospective) of one year duration found that the number of acute rejection episodes was significantly lower in the tacrolimus group compared with the ciclosporine group ( $p = 0.009$ ). In the tacrolimus group the acute rejection episodes happened 113 days after transplantation (mean time) while in the CsA – ME group the mean time was 60 days. The CsA – ME group presented steroid resistant rejections in the 10% of group population and it was necessary to give OKT3, while the tacrolimus group did not present steroid resistant rejections. The cost of hospital treatment was significantly higher in the CsA – ME group<sup>43</sup>. Finally, the TMC multicenter study after 12 month follow up concludes that the clinical outcome is better with tacrolimus based immunosuppression than with CsA ME<sup>44</sup>.

In a single center retrospective analysis of liver transplantation with nine year follow up, tacrolimus immunosuppression resulted better graft and patient survival rates, lower incidence of acute and corticosteroid – resistant rejection episodes and significantly fewer cases of retransplantation<sup>45</sup> but the ciclosporine formulation was not specified. Short-term results of multicenter prospective randomized trials comparing tacrolimus to CsA ME showed similar efficacy in terms of patient and graft survival but significantly lower rates of acute rejection and corticosteroid resistant rejection episodes<sup>46</sup>.

The Pittsburg study reported that liver re – trans-

plantation was necessary in 16 children of the 241 on CsA while no re – transplantation was noticed in 203 children on tacrolimus<sup>47</sup>. The same center reported steroid withdrawal in 90% of children on tacrolimus and 5% of children on cyclosporine<sup>48</sup>. Another study reported steroid withdrawal 48% versus 4.6 respectively<sup>49</sup>.

Basic problems that might have in mind transplant doctors in children liver transplantation are lymphoproliferative disease in cases on tacrolimus, and thrombotic microangiopathy, seizures and kidney fibrosis in cases on cyclosporine<sup>50</sup>.

### Tacrolimus in heart transplantation

The first information about tacrolimus in heart transplantation comes from Pittsburg where it was used originally as rescue therapy and later as basic immunosuppression<sup>51</sup>. In multicenter comparative studies between tacrolimus and cyclosporine A, in Europe and USA, no difference was noticed regarding the patient survival and the risk of heart allograft rejection<sup>52,53</sup>. Also there was no difference as far as the safety profile of the two drugs, the kidney function, the hyperglycemia, the hypomagnesemia or the hyperkalemia. The American Multicenter Study showed significantly lower rate of hypercholesterolemia needing therapy as well as significantly lower rate of new cases of hypertension in the tacrolimus group and the European Study showed that the need for antihypertensive agents was significantly lower in the tacrolimus group. A recent study with a three year patient follow up showed lower rejection rate in the tacrolimus group when compared with the cyclosporine group but there was no significant difference in patient survival. In this study the patients in the cyclosporine group presented augmented needs for diuretics while the patients in the tacrolimus group presented lower needs for statins and antihypertensive agents<sup>54</sup>. Patients on cyclosporine therapy with relapsing rejection episodes or rejections resistant to the classical antirejection treatment may need conversion from cyclosporine to tacrolimus<sup>55-57</sup>. As far as the quality of life of patients with heart transplantation tacrolimus based immunosuppression seems to be significantly better than CsA based immunosuppression in terms of time and extend of improvement<sup>58</sup>.

Tacrolimus basal immunosuppressive regimens compared with CsA ME basal regimens presented similar patient survival rates after 6-36 month follow up<sup>59,60</sup>. There were significantly fewer recurrent rejection episodes in the tacrolimus group and a tendency, not significant, for lower rates of acute rejection episodes in the same group.

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