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Switch to belatacept in kidney graft recipients

Cambio a belatacept en trasplante renal

Dear editor:

Calcineurin inhibitors (CNIs) are the gold standard immunosuppression in kidney transplant recipients. These drugs have shown better results in graft survival and patient outcome during the first year after transplantation. However, long-term use is associated with acute and chronic nephrotoxicity, which predisposes to graft loss.

Belatacept is a fusion protein binding to CD80 or CD86 ligands on antigen presenting cells that selectively blocks T-cell costimulatory signals. Data derived from two phase III trials (BENEFIT and BENEFIT-EXT) demonstrated the efficacy and safety of Belatacept in combination with Basiliximab, steroids and mycophenolic acid preventing graft acute rejection in Epstein–Barr virus positive recipients. Recently, the results of BENEFIT and BENEFIT-EXT study after 7 year follow up confirmed former data and showed a significant reduction in death and graft loss associated with the use of belatacept.[1]

Given the relevance of its beneficial effects in kidney function, some authors have proposed switching CNIs into belatacept treatment in intolerant patients to calcineurin or mTOR inhibitors showing an improvement in renal function.[2–5]

In our country, the administration of Belatacept is restricted by public health insurance. Public hospitals may use belatacept after individualized assessment requiring specific approval by internal committees in each case.

We summarize (Table 1) our clinical experience of switching to belatacept in 5 kidney transplant recipients through 2013–2015 after failure or intolerant therapy to tacrolimus and/or everolimus. All patients were Epstein–Barr virus positive.

Pre-transplant kidney biopsies were not performed. Clinical data were compatible with suboptimal donors, predisposing to a recipient poorer renal function. After transplantation patients received immunosuppression therapy consisting of anti-lymphocyte depleting antibodies, steroids and mycophenolic acid postponing tacrolimus starting to minimize delayed graft function. In four patients (cases 2, 3, 4 and 5) renal function was not adequate in the first month post-transplant. Analysis of graft biopsy showed CNI toxicity and chronic vascular lesions (likely related with donor background), but no evidence of acute rejection. Everolimus was considered an alternative to tacrolimus in all four cases. However it was not tolerated because of proteinuria or bone pain. In case 1 the reason for graft dysfunction was a thrombotic microangiopathy (TMA) due to the sequential use of tacrolimus first and cyclosporine later. They were converted to belatacept between 2 and 8 months post-transplantation

Table 1 – Description clinical cases.

	Patients				
	Case 1	Case 2	Case 3	Case 4	Case 5
Donor					
Age–yr	60	49	54	44	73
ECD/DCD/ARF	Yes/No/No	No/No/Yes	No/No/No	No/Yes/Yes	Yes/No/No
Recipient					
Age - yr	60	54	52	29	60
Sex	Male	Male	Female	Male	Male
Induction therapy	Polyclonal ATG	Polyclonal ATG	Polyclonal ATG	Thymoglobulin	Thymoglobulin
IS maintenance therapy	Steroids, MMF, Tacro 1st, Cyclo 2nd	Steroids, MMF, Tacro	Steroids, MMF, Tacro 1st, Ever 2nd	Steroids, MMF, Tacro 1st, Cyclo 2nd	Steroids, MMF, Tacro
Renal histology lesions prior to belatacept switch	TMA	Vascular lesions, benign HTN	Vascular lesions, CNI toxicity	Extensive ATN	Vascular lesions, IFTA, CNI toxicity
Time from Tx to switch (months)	2	2	8	6	6
Anti HLA antibodies					
Pre-conversion	Negative	Positive (class I)	Negative	Negative	Negative
Post-conversion	Negative	Negative	Negative	Negative	Negative
Creatinine (mg/dl)/CKD-EPI (ml/min)					
Pre-conversion	5.4/11.4	3/25.8	2.5/24.8	3.1/25.1	3.3/19
6 m post-conversion	2.29/30.7	2.1/35.2	1.5/35	1.9/47	2.7/25
12 m post-conversion	2.4/28.8	1.7/42	1.5/35.6	1.86/47	2.5/27
Proteinuria (g/24 h)					
Pre-conversion	0.42	1.7	0.3	0.17	0.7
6 m post	0.7	0.7	0.2	0.14	0.45
12 m post	0.4	0.4	NA	0.07	0.29
Acute rejection post-conversion	No	No	No	No	No

ECD, expanded criteria donor; DCD, donor after circulatory death; ARF, Acute renal failure; IS, immunosuppression; Tx, transplantation; TMA, thrombotic microangiopathy; CNI, calcineurin inhibitors; HTN, arterial hypertension; ATN, acute tubular necrosis; IFTA, interstitial fibrosis and tubular atrophy; Tacro, Tacrolimus; Cyclo, Cyclosporine; Ever, Everolimus; MMF, mycophenolate mofetil; NA, not available.

showing immediate improvement of kidney function. Furthermore, anti HLA antibodies were negative after one year post-conversion.

Patients with low immunological risk (cases 1, 3, 4 and 5) received belatacept at a less intense dosage[5] and in case 2 the dosage of belatacept was more intense[5] due to positive class I anti-HLA antibodies (no donor specific antibodies).

All together, switching to belatacept is effective and safe in patients with failure therapy and/or intolerant to calcineurin or mTOR inhibitors at distinct time periods since transplantation. Moreover, belatacept was associated with better kidney function with no adverse events at short term and is an excellent alternative in grafts with renal dysfunction due to chronic vascular lesions or to CNI-TMA. This positive experience requires long-term assessments to confirm improvement in graft outcome.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Non-critical urinary cadmium excretion as a risk factor associated with tubular markers of early kidney injury in Central Mexico

Niveles no-críticos de excreción urinaria de cadmio como factor de riesgo asociado con marcadores tubulares de daño renal temprano en la región central de México

Dear Editor:

Cadmium (Cd) is an ubiquitous element in nature and high levels of Cd exposure is considered a risk factor for renal injury; however, their nephrotoxic effects at low-environmental exposure levels are debated.[1,2]

Cd accumulates in the proximal tubule renal cells where inhibits the mitochondrial respiratory chain and this results in mitochondrial dysfunction and free radical formation.[3]

Some of the urinary markers used to evaluate Cd nephrotoxicity are N-acetyl-β-D-glucosaminidase (NAG), α1-microglobulin (α1M), β2-microglobulin (β2M) and the kidney injury molecule (KIM-1).[4] The aim of this study was to search for the effects of urinary cadmium excretion on markers of early renal injury in population living in suburban communities in central Mexico.

The study was done in 7 communities located close to Queretaro city in Central Mexico; farming and agricultural practices are common but these areas are rounded by manufacturing activities. We evaluated 90 voluntary healthy subjects (≥20 years old), using a simple probabilistic sampling procedure on every of the communities studied. Those with current urinary tract infection, previous diagnosis of kidney disease, liver disease, cancer, or other chronic disease, as well as pregnant women were excluded.

A questionnaire was used to obtain information on personal health history, and risk factors to Cd exposure. Blood pressure measurements were obtained with an aneroid sphygmomanometer after a 5 min resting in sitting position, and blood samples were taken after a fasting ≥8 h during the same visit.

GFR was calculated with the CKD-Epi formula and spot urine samples for albumin, α1-microglobulin and cadmium analysis were collected in cadmium-free containers. Albumin and α1M were creatinine adjusted.

Cd measurements were done at the Department of Environmental Toxicology Laboratory (San Luis Potosi Medical School); and quantification was carried out with a Perkin-Elmer 3110 atomic absorption spectrometer.[5]

We categorized urinary Cd excretion in two groups according to CdU excretion and multivariate analysis was performed to identify risk factors for high Cd levels, albuminuria and higher urinary α1M. A p value ≤0.05 was considered as statistically significant and data were analyzed using the SPSS 23.0 software.

The overall analysis included 90 adults with no antecedent of occupational exposure to Cd, 66.6% of all participants were women and the mean age was 41 ± 12 years; CdU median levels were 0.37 ± 0.41 μg/gCr and few patients (n = 3) had CdU ≥1 μg/gCr.

Those subjects with CdU ≥ 0.37 μg/gCr had higher levels of α1M (9.4 ± 9 vs 3.2 ± 4 μg/gCr, p = 0.001) and albumin excretion (13.1 ± 24 vs 3.9 ± 2.5 g/gCr, p = 0.001). Those patients with higher CdU excretion had a higher risk for α1M ≥ 10 (OR 5.0, CI95 1.4–18.6, p = 0.01) and micro-albuminuria (OR 20, CI95 1.0–39, p = 0.04).

In multivariate analysis, CdU was the most important risk factor associated with higher α1M excretion and albuminuria after adjustments for age, BMI, smoking status, blood pressure, lead concentration and GFR.

In non-smoking subjects, those with CdU ≥ 0.37 μg/gCr had higher urinary excretion of α1M (7.5 ± 7.2 vs 3.3 ± 4.7 μg/gCr, p = 0.002) and albumin (11.1 ± 18 vs 3.9 ± 2.5 g/gCr, p = 0.003); CdU was associated with a higher risk for α1M ≥ 10 μg/gCr (OR 4.1, CI95 1.1–19, p = 0.03), and CdU was the most important factor associated with higher α1M excretion.