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Original article

Intermediate steroid withdrawal after renal transplantation and anti-HLA antibodies (HLA-Abs) development

Elena Monfá[a,*], *David San Segundo*[b,d], *Juan Carlos Ruiz San Millán*[a], *Judith Sanabria*[c], *Zoila Albines*[a], *Emilio Rodrigo*[a], *Iñigo Romón*[d], *Esther Asensio*[b,d], *Manuel Arias*[a], *Marcos López-Hoyos*[b,d]

[a] *Nephrology Department, Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander, Spain*
[b] *Immunology Department, Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander, Spain*
[c] *Pharmacology Department, Hospital Universitario Marqués de Valdecilla-IDIVAL, Santander, Spain*
[d] *Histocompatibility Testing Laboratory, Hospital Universitario Marqués de Valdecilla, Santander, Spain*

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ABSTRACT

Introduction: Steroid withdrawal in renal transplantation is desirable to avoid their adverse effects. However, by decreasing the immunosuppression, could lead to an increased risk for the development of HLA-Abs.

Objective: Evaluate the relationship between steroid withdrawal and development of HLA-Abs in renal transplantation.

Methods: We analyzed sera by Luminex from 182 kidney transplants performed from 1998 to 2011, before and two years after transplantation. All the patients had a pretransplant PRA (panel reactive of antibodies) <20% by complement-dependent cytotoxicity (CDC) and maintenance immunosuppression with tacrolimus and mycophenolate mofetil (MMF). We compared a group of steroid withdrawal at 7 months (group-I; $n = 130$) and another control with non-withdrawal (group-II; $n = 52$).

Results: 22 patients (16.9%) in group-I and 11 patients in group-II (21.1%) had HLA-Abs after two years (pNS). Despite excluding patients with PRA >20%, we detected HLA-Abs pretransplant by Luminex in 11.5% of patients in both groups, of which, 66.6%, versus 53% (p 0.058), developed new specificities, with a similar percentage of donor specific antibodies (DSA) in both groups (33.33% vs 36.36%), pNS. In the subgroup without pretransplant HLA-Abs (group-I; $n = 115$, group-II; $n = 45$), 6.08% developed de novo HLA-Abs, being DSA 3.4% (Group-I) versus 7.69% in group II with 3.84% DSA (pNS).

Conclusions: Steroid withdrawal at 7 months of renal transplantation does not entail a higher risk in terms of HLA-Abs development in patients without pretransplant HLA-Abs and treatment with tacrolimus and MMF, although larger studies are needed to confirm these findings.

* *Corresponding author.*
E-mail address: elenamonfa@gmail.com (E. Monfá).
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Retirada intermedia de esteroides después del trasplante renal y desarrollo de anticuerpos anti-HLA (Ac-antiHLA)

Palabras clave:
Trasplante renal
Inmunosupresión
Retirada
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RESUMEN

Introducción: La retirada de esteroides en el trasplante renal es deseable por sus efectos adversos, sin embargo, al disminuir la inmunosupresión podría conllevar un riesgo superior para el desarrollo de Ac-anti-HLA.

Objetivo: Evaluar la relación entre la retirada de esteroides y el desarrollo de Ac-anti-HLA en el trasplante renal.

Métodos: Se evaluaron los sueros por Luminex de 182 trasplantados renales desde 1998 a 2011, antes y a los 2 años del trasplante. Todos tenían un panel reactivo frente a anticuerpos (PRA) < 20% pretrasplante por citotoxicidad dependiente de complemento y mantuvieron la inmunosupresión con tacrolimús y micofenolato mofetilo (MMF). Comparamos un grupo de retirada de esteroides a los 7 meses (grupo I; n = 130) y otro de no retirada (grupo II; n = 52).

Resultados: 22 pacientes (16,9%) en el grupo I y 11 pacientes en el grupo II (21,1%) presentaban Ac-anti-HLA a los 2 años (pNS). A pesar de excluir a los pacientes con PRA > 20%, detectamos Ac-anti-HLA pretrasplante por Luminex en el 11,5% de los pacientes en ambos grupos, de los cuale, desarrollaron nuevas especificidades el 66,6% del grupo I y el 53% en el grupo II (p 0,058), con un similar porcentaje de anticuerpos donante específicos (DSA) (33,3% vs. 36,36%), pNS. En el subgrupo sin Ac-anti-HLA pretrasplante (grupo I; n = 115; grupo II; n = 45), el 6,08% desarrollaron Ac-anti-HLA de novo, siendo DSA el 3,4% (grupo-I) vs. 7,69% con DSA en el 3,84% (grupo-II), pNS.

Conclusiones: La retirada de esteroides a los 7 meses del trasplante renal no conlleva un riesgo superior en términos de desarrollo de Ac-anti-HLA en aquellos pacientes sin anticuerpos pretrasplante y en tratamiento con tacrolimús y MMF, aunque se requieren estudios más amplios para confirmar estos hallazgos.

Introduction

The detection of antibodies against the HLA system (HLA-Abs) in transplantation has been linked to the development of acute and chronic antibody mediated rejection (ABMR)[1] in clinical and subclinical forms of presentation, and remains as a major cause of graft losses.[2] Monitoring HLA-Abs has become a routine practice in the clinical follow up of renal transplant recipients[3] that helps to indicate a graft biopsy and early treatment.

The development of de novo HLA-Abs is usually associated with modifications in the immunosuppressive treatment. In clinical practice, the modulation of the immunosuppressive regimen is common in order to avoid the long-term adverse effects. The calcineurin inhibitors (CNI) withdrawal or conversion to mTOR-inhibitor is currently performed to reduce nephrotoxicity or risk of malignancy.[4,5] These changes in immunosuppression are risk of development of new HLA-Abs and consequently ABMR.[6,7]

The steroids withdrawal is also desirable to avoid their adverse effects on long-term treatment, but its relationship with the development of new HLA-Abs is not yet well established.

One of the most important adverse effects of steroids is increased cardiovascular risk. The steroid maintenance has been linked to the onset of diabetes mellitus, dyslipidemia, hypertension and obesity.[8,9] In a study involving 68,781 patients who received prednisone versus 82,200 patients who did not, it was observed that the patients who received doses of prednisone ≥7.5 mg/day had a relative risk of 2.5 for cardiovascular events.[10] In addition, the rate of death with a functioning graft is high (40%) being cardiovascular events the most frequent cause.[11] Therefore, the maintenance of steroids could be a modifiable cause of death with a functioning graft.

Currently, there are potent immunosuppressants in maintenance therapy (Tacrolimus and Mycophenolic mofetil-MMF) and the steroids withdrawal seems plausible, at least in those patients with low immunological risk. Steroids withdrawal has risk of acute rejection and higher slope of glomerular filtration rate (GFR) loss in the long term. We hypothesize that steroids elimination can contribute to production of donor specific antibodies (DSA). So, the aim of our study is to assess the relationship between steroid withdrawal and development of HLA-Abs after renal transplantation.

Material and methods

Patients

We studied 652 kidney transplant recipients, performed in University Hospital Marqués de Valdecilla, Santander (Spain) from January 1998 to December 2011 who met the following criteria: graft survival of at least two years and maintenance of immunosuppression with tacrolimus and MMF during the

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