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Brief review

Lymphocyte-depleting induction and steroid minimization after kidney transplantation: A review

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ABSTRACT

Steroid minimization after kidney transplantation has become more widely practiced as transplant clinicians seek the potential benefits such as reduced cardiovascular risk factors, improved growth in pediatric patients, and improved compliance with the immunosuppression regimen. Steroid avoidance (i.e. no steroids after the first week) is generally favored compared to later withdrawal. Induction therapy is routine in this setting, frequently rabbit antithymocyte globulin (rATG, Thymoglobulin®) or off-license use of alemtuzumab. Direct comparisons of steroid minimization regimens versus standard steroid regimens are rare. However, the available data show that the risk of acute rejection is low when rATG or alemtuzumab induction is given to support steroid-avoidance regimens after kidney transplantation. Steroid avoidance may be inadvisable in patients at high immunological risk or at risk of recurrent glomerular disease. Steroid withdrawal after day 8 may be possible without additional risk of rejection in patients given rATG induction, but while encouraging, the data are too sparse for firm conclusions. In summary, steroid avoidance may be beneficial for patients after renal transplantation, with the potential to avoid or reduce steroid-related

Abbreviations: ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; BPAR, biopsy-proven acute rejection; CI, confidence interval; CNI, calcineurin inhibitor; CsA, cyclosporine; DSA, donor-specific antibody; HR, hazard ratio; IL-2R, interleukin 2 receptor; KDIGO, the Kidney Disease: Improving Global Outcomes; MMF, mycophenolate mofetil; NODAT, new-onset diabetes mellitus; OPTN, Organ Procurement and Transplantation Network; PRA, panel reactive antibodies; rATG, rabbit antithymocyte globulin.

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comorbidities. Whilst depleting induction therapy could be the treatment of choice, results of prospective randomized, controlled studies are eagerly awaited.

Inducción con anticuerpos antilinfocitarios y minimización de esteroides en trasplante renal

Palabras clave:
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Trasplante renal
ATG
Glomulina antitimocítica de conejo
Timoglobulina
Alemtuzumab

RESUMEN

La minimización de esteroides después del trasplante renal constituye una práctica muy extendida en la búsqueda de potenciales beneficios cardiovasculares, mejor crecimiento en pacientes pediátricos o aumento de la adherencia al tratamiento inmunosupresor. El uso de inducción depletiva con ATG de conejo o alemtuzumab puede contribuir a evitar el uso de esteroides o, al menos, a permitir su suspensión precoz. Esta estrategia se ha revisado en la literatura, añadiendo la opinión de expertos al análisis. La suspensión de esteroides muy precoz (antes de la primera semana) parece preferirse a la suspensión más tardía. En ese contexto, la inducción preventiva es la práctica más utilizada, habitualmente con globulina antitimocítica de conejo (rATG, timoglobulina) o alemtuzumab (en uso fuera de indicación). Son raras las comparaciones directas de los regímenes de minimización de esteroides con los de uso estándar. Sin embargo, los datos disponibles muestran que el riesgo de rechazo agudo es bajo cuando se administra rATG o alemtuzumab para facilitar la suspensión muy precoz de esteroides. Esta práctica puede ser menos aconsejable en pacientes con alto riesgo inmunológico o predispuestos a una recurrencia de la enfermedad glomerular de base. La suspensión de esteroides a partir del día 8 es factible sin que el riesgo de rechazo aumente en pacientes tratados con rATG. No obstante, y aunque los datos disponibles así lo indican, requieren confirmación definitiva. En conclusión, la minimización extrema de esteroides puede ser beneficiosa en pacientes que reciben un trasplante renal, con la ventaja que supone evitar o reducir la comorbilidad asociada con ese tratamiento. Si bien la inducción depletiva podría ser el tratamiento de elección en ese contexto, son necesarios nuevos ensayos aleatorizados controlados que lo confirmen.

Introduction

Steroid-sparing immunosuppressive regimens are widely used after kidney transplantation as clinicians seek to minimize steroid-related adverse events.[1] Rapid steroid discontinuation lowers the rates of cataracts, vascular necrosis and cytomegalovirus infection[2] and may improve growth in children.[3] Cardiovascular benefits are less well established, although positive effects have been observed for lipid profile and weight gain.[4,5] Generally, it is difficult to demonstrate differences in randomized trials in unselected populations, and studies of steroid minimization regimens have often not reported steroid-related side effects, or were underpowered to demonstrate a significant difference. However, even if data remain unconvincing about reduced cardiovascular risk, the non-cardiovascular side effects of chronic steroid therapy require costly management[6] and some, such as weight gain, can adversely affect patient compliance[7,8] with potential consequences for graft outcomes.

Strategies for steroid minimization comprise either '*steroid avoidance*' (or '*steroid-free*') regimens, which will be defined here as no intravenous (i.v.) or oral steroids after the first 1–2 weeks post-transplant, or *steroid withdrawal*, i.e. steroid discontinuation after weeks 1–2.[4,9,10]

Steroid avoidance protocols have become increasingly popular in recent years. Steroid-free immunosuppression without induction therapy has been attempted after kidney transplantation using a calcineurin inhibitor (CNI)-based maintenance regimen, but randomized trials showed acute rejection to be significantly more frequent[4,11,12] or more severe[13] than with standard steroids. A series of randomized trials comparing steroid avoidance versus ongoing steroid therapy in selected populations receiving interleukin-2 receptor (IL-2R) induction have reported mixed results.[14–18] High rates of biopsy-proven acute rejection (BPAR) were observed in the FREEDOM study for patients given basiliximab induction with cyclosporine (CsA), mycophenolic acid (MPA) and either a single i.v. dose of steroids (31.5% BPAR at 1 year) or steroids to day 7 (26.1%).[19] Other researchers have found no significant effect on BPAR

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