http://www.revistanefrologia.com

Immunosuppression of the living-donor recipient

Julio Pascual Santos[1], Domingo Hernández Marrero[2]

[1] Nephrology Department. Mar Hospital, University of Barcelona, Barcelona, Spain

[2] Nephrology Department. Carlos Haya University Regional Hospital, Malaga, Spain

Nefrologia 2010;30(Suppl. 2):80-4

doi:10.3265/Nefrologia.pre2010.Nov.10694

ABSTRACT

Living donor kidney transplantation allows immunosuppression individualization based on clinical and immunological criteria.

Living donor kidney transplantation allows administration of immunosuppressive drugs days before transplantation, for a better acute rejection prevention.

In recipients HLA-identical related to the donor, a tacrolimus-micophenolic acid régimen is recommended. Tacrolimus withdrawal after 6 months may be advisable.

In all non-HLA-identical recipients, basiliximab induction is recommended, with the exception of high immunological risk patients, in whom thymoglobulin is a better option.

The use of a kidney from an expanded criteria donor might imply a reduction in tacrolimus exposure since the very beginning, to optimize kidney graft function.

In general, and depending on immunological risk, steroid withdrawal after the first 3 to 6 months is recommended.

ABO-incompatible living donor kidney transplantation is feasible after specific immunoadsorption, gammaglobulins, a dose of rituximab and conventional immunosupression.

Inmunosupresión del receptor de donante vivo

RESUMEN

El trasplante renal de donante vivo permite una individualización de la inmunosupresión en función de criterios clínicos e inmunológicos.

El trasplante renal de donante vivo permite la administración de agentes inmunosupresores días antes del trasplante y prevenir así mejor el rechazo agudo. En los receptores HLA idénticos relacionados a su donante, se recomienda iniciar la pauta con tacrolimus y un derivado de ácido micofenólico y valorar la suspensión de tacrolimus a partir del sexto mes.

En todos los receptores que no son HLA-idénticos a su donante, se recomienda inducción con anticuerpos frente al receptor de interleuquina-2 (basiliximab), excepto en aquellos de alto riesgo inmunológico, en los que se recomienda timoglobulina.

La utilización de un riñón procedente de un donante con criterios expandidos requiere reducir la dosis habitual de tacrolimus para optimizar la función renal.

En general, y dependiendo del riesgo inmunológico, se recomienda la suspensión de los esteroides a partir del mes 3-6 postrasplante.

El trasplante renal de donante vivo ABO-incompatible es posible mediante la realización de inmunoadsorción específica, administración de gammaglobulinas, dosis única de rituximab e inmunosupresión convencional.

INTRODUCTION

Living-donor kidney transplantation (LDKT) is the treatment of choice for patients with advanced CKD. Success depends mainly on selecting the best possible donor, the rigorous search for and identification of recipient comorbidity and the possibility of advance immunosuppression (2 to 3 days before LDKT) based on the biological characteristics of the donor-recipient pair.[1] These patients are not exempt from early immune dysfunctions and are exposed to the effects of chronic graft dysfunction and the irreversible loss of kidney function over the long term. Therefore, these patients should receive individualised immunosuppression with the aim of optimising results. However there is not enough convincing evidence to indicate the best treatment strategies to follow.

Correspondence: Julio Pascual Santos
Servicio de Nefrología. Hospital del Mar. Parc de Salut Mar.
Passeig Marítim, 25-29. 08003 Barcelona. Spain.
julpascual@gmail.com

In this review, we present the available information, based on the best evidence and the opinion of experts, regarding the ideal initial immunosuppression and maintenance in patients with LDKT in the following clinical scenarios: *1)* HLA-identical donor-recipient; *2)* non-HLA-identical donor-recipient; *3)* living-donor with isolated medical abnormalities (expanded donor); *4)* recipient with high immunological risk, and *5)* ABO-incompatible donor-recipient.

HLA-IDENTICAL DONOR-RECIPIENT

Identical twins

Although very infrequent in practice, this is the ideal situation in terms of the need for pharmacological immunological suppression, which would be minimal. Guidelines in this context vary from no immunosuppression to more conventional approaches and early tapering. A review of clinical experience reveals that this type of recipient receives more immunosuppression than is theoretically necessary.[2]

Recommended approach:

1. A single perioperative dose of steroids (e.g., 125mg IV).
2. Only steroids for one week (0.25mg/kg/day).
3. Mycophenolate mofetil (MMF, 1g every 12 hours) or sodium mycophenolate (MFS, 720mg every 12 hours) for 8-12 weeks, tapering until withdrawal.

HLA-identical relative but not identical twins

Less than 5% of LDKT correspond to this profile.[3,4]

Recommended approach:

1. A single perioperative dose of steroids (e.g., 125mg IV).
2. Only steroids for one week (0.25mg/kg/day).
3. Low-dose tacrolimus (0.05mg/kg/day, levels of 4-7ng/ml) beginning 3 days before LDKT and maintaining treatment for 6 months.
4. MMF (1g every 12 hours) or MFS (720mg every 12 hours).

At this point tacrolimus can be stopped, maintaining only the treatment with MMF/MFS over the long term to prevent chronic calcineurin-inhibitor toxicity. The suppression of production of IL-10 and the absence of dendritic cell maturation in patients that only receive the antiproliferative drugs (MMF/MFS) support this approach.

Another alternative is to administer low doses of an mTOR inhibitor (sirolimus or everolimus, from day 1-2 post-transplant, levels of 3-8ng/ml), instead of MMF/MFS. However, there is less experience with this approach.

It is not necessary to administer monoclonal (anti-CD25) or polyclonal antibodies, except in cases of high immunological risk or other clinically unfavourable situations, as we will explain further on.

NON-HLA-IDENTICAL DONOR-RECIPIENT

Even if there is no identical HLA compatibility between donor and recipient, some patients may share an HLA haplotype (locus A, B, and DR) when genetically related to their donor (between brothers or between parents and children). In this case, moderate immunosuppression may be adequate, except in cases of greater immunological risk.

Recommended approach:

1. Induction with basiliximab (Simulect®) at a dose of 20mg on days 0 and 4 post-transplant. This induction is associated with a significant decrease in the incidence of acute rejection[6,7] and short-term survival.[7]
2. Initial intraoperative administration of 250mg IV corticosteroids and subsequent administration of 0.25mg/kg/day for 2 weeks with gradual tapering, suspension should be considered from the third month post-transplant.
3. Tacrolimus 0.1mg/kg/day, levels of 4-7ng/ml, beginning 3-4 days before the transplant and maintaining indefinitely. During the first three months, maintain dose close to 7ng/ml, to be tapered later.
4. MMF (2g/day) or MFS (1.44g/day) for the first 2-4 weeks and later MMF 1g/day or MFS 720mg/day.

As an alternative to basiliximab, induction can be carried out for 3-5 days with polyclonal antibodies (thymoglobulin) at doses of 1-1.25mg/kg/day, which is associated with a reduction in the rate of acute rejection without an increase in costs or post-transplant complications.[8] A similar approach can also be used when the donor has isolated medical abnormalities or meets expanded donor criteria (advance age, hypertension, obesity, albuminuria, metabolic syndrome, etc.)

as we will see below. Induction with alemtuzumab is associated with greater early rejection of grafts than induction with basiliximab.[9]

LIVING-DONOR WITH ISOLATED MEDICAL ABNORMALITIES (LIVING-DONOR MEETING EXPANDED CRITERIA)

This situation occurs when the donor has some medical complexity that may complicate evolution in the long term (advanced age, hypertension, obesity, microhaematuria, nephrolithiasis, metabolic syndrome or a reduced glomerular filtration rate), but still compatible with LDKT. Observational studies and a recent systematic review of this type of donor have not shown a greater risk of chronic renal failure for the donor and the recipient than in the general population.[10,11]

Generally, these patients should receive induction with basiliximab or polyclonal antibodies (thymoglobulin), with later introduction of tacrolimus or with low doses of it from the start, a full-dose of an antiproliferative drug, and eventually a change from tacrolimus to an mTOR inhibitor at the third month post-transplant, as the clinical situation allows.

Recommended approach:

1. Perioperative steroids (250mg IV) on the day of the transplant and subsequent 0.25mg/kg/day for 2 weeks, tapering until suspension at the third month post-transplant.

2. Induction with 20mg basiliximab on days 0 and 4 post-transplant, or 3-5 doses of thymoglobulin of 1-1.25mg/kg/day beginning the day of the LDKT.

3. Tacrolimus at the fourth or fifth day post-transplant at doses of 0.05mg/kg/day (levels of 4-7ng/ml) when thymoglobulin is used, or the same doses from day 0 when basiliximab is used.

4. MMF 2g/day or MFS 1.44mg/day for the first 2-4 weeks and later MMF 1g/day or MFS 720mg/day.

5. In certain cases, a change from tacrolimus to sirolimus or everolimus at the third month may be beneficial, to maintain levels of 5-8ng/ml for the first year post-transplant and 3-7ng/ml later.

RECIPIENT WITH HIGH IMMUNOLOGICAL RISK

This situation occurs when patients have a high rate of preformed anti-HLA or donor-specific antibodies (PRA>50%), re-transplants, loss of previous graft due to immunological dysfunction during the first year and positive crossmatches.[12] These patients should receive immunosuppression similar to those patients at immunological risk who receive a kidney transplant from a deceased donor.[12-14]

Recommended approach:

1. Perioperative corticosteroids (250-300mg IV). Subsequently, 0.25mg/kg/day for the first month, with later tapering to reach a dose of prednisone of 5-7.5mg/day at the sixth month post-transplant. Eventually, the withdrawal of steroids can be considered, especially in those who have not suffered immunological dysfunction.

2. Induction with thymoglobulin, five doses of 1-1.25mg/kg/day.

3. Tacrolimus, 0.15mg/kg/day from 3 days before the transplant to maintain levels of 8-12ng/ml for the first 6 months and later, as the clinical situation allows, maintain levels of 4-7ng/ml.

4. MMF 2g/day or MFS 1,440mg/day with adjustments based on tolerance.

An alternative approach could be:

1. Perioperative corticosteroids (250-500mg IV). Subsequently, 0.25mg/kg/day for the first month, with later tapering to reach a dose of prednisone of 5-7.5mg/day at the sixth month post-transplant.

2. Induction with thymoglobulin, five doses of 1-1.25mg/kg/day.

3. Tacrolimus, 0.15mg/kg/day from 3 days before the transplant to maintain levels of 8-12ng/ml until the introduction of sirolimus or everolimus on the fourth day post-transplant. From then on, levels of tacrolimus will be maintained at 4-7ng/ml.

4. Sirolimus or everolimus from the fourth day post-transplant, levels of 3-7ng/ml.

Donors with medical abnormalities should be avoided with these patients. Similarly, on suspicion of immunological dysfunction, a graft biopsy should be performed and, based on histological findings, an increase in the maintenance doses of immunosuppressants should be considered.

ABO INCOMPATIBLE DONOR-RECIPIENT

In this case, it is of primary importance to determine the immunological risk of the donor-recipient pair, analysing the

hemagglutinin titre, HLA sensitivity (PRA, both by cytotoxicity mediated by complement as well as by flow cytometry) and the donor-specific flow cytometric crossmatch (CD3 and CD20 by flow cytometry).

The elimination or at least the significant reduction of hemagglutinins is essential.[15-18] B-cell ablative therapy (better with rituximab than splenectomy[15-17]) is essential for some groups but not for others.[18]

Recommended approach:

1. Perioperative corticosteroids (250-500mg IV). Subsequently, 0.25mg/kg/day for the first month, with later tapering to reach a prednisone dose of 5-7.5mg/day at the sixth month post-transplant.

2. Anti-lymphocyte induction according to previous immunological risk (re-transplant, sensitivity, etc): basiliximab if the risk is normal or low, and thymoglobulin if PRA>50%.

3. Rituximab 375mg/m^2, single dose, 8-10 days before the transplant.

4. Immunoadsorption with specific carbohydrate columns (Glycosorb), 2 plasma volumes:

   a) Four or five pre-transplant sessions (days -5, -4, -2, -1 if four are done and -7, -6, -5, -3, -1 if five are done), if reaching adequate hemagglutinin titres (IgG<16).

   b) Three post-transplant sessions (days +2, +4, +7). More sessions will be needed if the hemagglutinin titre increases.

   c) Polyclonal gamma globulin 250mg/kg, two doses (days -4 or -5 and -1) after the relevant pre-transplant immunoadsorption sessions.

   d) MMF 2g/day or MFS 1,440mg/day from day 8 pre-transplant and for 3 months, later tapering based on tolerance.

5. Tacrolimus, 0.15mg/kg/day from 3 days before the transplant to maintain levels of 8-12ng/ml for the first 6 months and later, as the clinical situation allows, maintain levels of 4-7ng/ml.

Treatment for acute rejection, in addition to steroids and (if Banff grade II-III): thymoglobulin, along with the immunoadsorption sessions based on the hemagglutinin titre.

REFERENCES

1. Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, et al. The medical evaluation of living kidney donors: a survey of US transplant centers. Am J Transplant 2007;7:2333-43.
2. Kessaris N, Mukherjee D, Chandak P, Mamode N. Renal transplantation in identical twins in United States and United Kingdom. Transplantation 2008;86(11):1572-7.
3. Walker JK, Alloway RR, Roy-Chaudhury P, Mogilishetty G, Cardi MA, et al. A prospective trial of a steroid-free/calcineurin inhibitor minimization regimen in human leukocyte antigen (HLA)-identical live donor renal transplantation. Transplantation 2009;87:408-14.
4. Van de Wetering J, Gerrits JH, van Besouw NM, Ijzermans JN, Weimar W. Successful tapering of immunosuppression to low-dose monotherapy steroids after living-related human leukocyte antigenidentical renal transplantation. Transplantation 2009;87:740-4.
5. Gerrits JH, Van de Wetering J, Weimar W, Van Besouw NM. T-cell reactivity during tapering of immunosuppression to low-dose monotherapy prednisolone in HLA-identical living-related renal transplant recipients. Transplantation 2009;87:907-14.
6. Gralla J, Wiseman AC. The Impact of IL2ra Induction Therapy in Kidney Transplantation Using Tacrolimus- and Mycophenolate-Based Immunosuppression. Transplantation 2010;90(6):639-44
7. Lim WH, Chang SH, Chadban SJ, Campbell SB, Dent H, et al. Interleukin-2 receptor antibody reduces rejection rates and graft loss in live-donor kidney transplant recipients. Transplantation 2009;88(10):1208-13.
8. Miller JT, Collins CD, Stuckey LJ, Luan FL, Englesbe MJ, et al. Clinical and economic outcomes of rabbit antithymocyte globulin induction in adults who received kidney transplants from living unrelated donors and received cyclosporine-based immunosuppression. Pharmacotherapy 2009;29:1166-74.
9. Sampaio MS, Kadiyala A, Gill J, Bunnapradist S. Alemtuzumab versus interleukin-2 receptor antibodies induction in living donor kidney transplantation. Transplantation 2009;88(7):904-10.
10. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, et al. Long-term consequences of kidney donation. N Engl J Med 2009;360:459-69.
11. Young A, Storsley L, Garg AX, Treleaven D, Nguan CY, et al. Health outcomes for living kidney donors with isolated medical abnormalities: a systematic review. Am J Transplant 2008;8:1878-90.
12. European Best Practice Guidelines for Renal Transplantation (Part 2). Nephrol Dial Transplant 2002;17(Suppl. 4):8-11.
13. Klem P, Cooper JE, Weiss AS, Gralla J, Owen P, et al. Reduced dose rabbit anti-thymocyte globulin induction for prevention of acute rejection in high-risk kidney transplant recipients. Transplantation 2009;88:891-6.
14. Padiyar A, Augustine JJ, Hricik DE. Induction antibody therapy in kidney transplantation. Am J Kidney Dis 2009;54:935-44.
15. Tanabe K, Ishida H, Shimizu T, Omoto K, Shirakawa H, et al. Evaluation of two different preconditioning regimens for ABO-incompatible living kidney donor transplantation. A comparison of splenectomy vs. rituximab-treated non-splenectomy preconditioning regimens. Contrib Nephrol 2009;162:61-74.

16. Wilpert J, Fischer KG, Pisarski P, Wiech T, Daskalakis M, et al. Longterm outcome of ABO-incompatible living donor kidney transplantation based on antigen-specific desensitization. An observational comparative analysis. Nephrol Dial Transplant 2010;25(11):3778-86
17. Oppenheimer F, Revuelta I, Serra N, Lozano M, Gutiérrez-Dalmau A, Esforzado N, et al. ABO incompatible living donor kidney transplantation: a dream come true. Experience of Hospital Clínic of Barcelona. Nefrologia 2010;30(1):54-63.
18. Montgomery RA, Locke JE, King KE, Segev DL, Warren DS, et al. ABO incompatible renal transplantation: a paradigm ready for broad implementation. Transplantation 2009;87(8):1246-55.

Sent for review: 1 Nov. 2010 | Accepted: 9 Nov. 2010